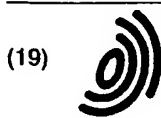


05/14068



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) **EP 1 217 066 A1**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
26.06.2002 Bulletin 2002/26

(51) Int Cl.7: **C12N 15/11, C07K 14/705,
A61K 38/17, G01N 33/68**

(21) Application number: **00870316.7**

(22) Date of filing: **21.12.2000**

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR**
Designated Extension States:
AL LT LV MK RO SI

(74) Representative: **De Clercq, Ann et al
De Clercq, Brants & Partners cv.,
Edgard Gevaertdreef 10a
9830 Sint-Martens-Latem (BE)**

(71) Applicant: **UNIVERSITEIT GENT
9000 Gent (BE)**

Remarks:

The sequence listing, which is published as annex to the application documents, was filed after the date of filing. The applicant has declared that it does not include matter which goes beyond the content of the application as filed.

(72) Inventor: **The designation of the inventor has not yet been filed**

(54) **Modulation of ATP-binding cassette transporter activity**

(57) The invention relates to the field of ATP-Binding Cassette (ABC) transporter molecules. and to molecules selectively modulating the activity of said ABC transporters. Herein are provided molecules and compounds which selectively modulate the activity of specific

ABC transporters. The invention also relates to molecules, compounds and compositions for preventing, treating or alleviating cancer or diseases related to bacterial, fungal or protozoal infections.

EP 1 217 066 A1

Description

FIELD OF THE INVENTION

- 5 [0001] The invention relates to the field of ATP-Binding Cassette (ABC) transporter molecules and to molecules selectively modulating the activity of said ABC transporters.

BACKGROUND OF THE INVENTION

- 10 [0002] The ATP-binding cassette (ABC)-transporters constitute one of the largest and most highly conserved protein super families, which are found in large numbers in all organisms (Holland and Blight, 1999). These transmembrane proteins transport a wide range of compounds through biological membranes. The ABC transport proteins can import essential nutrients into cells, such as ions, sugars, amino acids etc... ABC-transporters can further protect cells by exporting a wide range of toxic compounds, signal the presence of infectious agents, and regulate development in microorganisms and mammals (Higgins, 1992). ABC-transporters participate in the regulation of several tissues such as the liver, lungs, retina and the immune system (Holland and Blight, 1999; Higgins, 1992). Consequently, mutations affecting ABC-transporters are associated with a variety of human inherited diseases, including the cystic fibrosis transmembrane conductance regulator (CFTR) linked to cystic fibrosis (Sheppard and Welsh, 1999), and the ABC-A1 transporter linked to Tangier Disease (Rust *et al.*, 1999; Bodzioch *et al.*, 1999; Brooks-Wilson *et al.*, 1999). Disease treatment is also dependent upon the function of ABC-transporters. For example in cancer treatment, expression of the P-glycoprotein or MDR1 (multidrug resistance gene product) in cancer cells, confers multidrug resistance against chemotherapeutic agents and decreases the efficacy of treatment (Borst *et al.*, 1986; Hipfner *et al.*, 1999). The resistance of some bacteria to certain classes of antibiotics can be attributed to the activity of transmembrane ABC transporters (Higgins, 1992).
- 25 [0003] ABC-transporters consist of at least two basic subunits : an ATPase domain (also named NBD (domain) or (nucleotide binding domain)) which provides the energy required for the transport function, and a domain composed of six membrane-spanning helices, which form a channel and confer substrate specificity. Most ABC-transporters function as oligomers consisting of two ATPase and two transmembrane domains, which are either encoded separately, or tandemly replicated within a single polypeptide (Fig. 1). The transport of compounds across the membrane is accompanied by ATP hydrolysis. The ATPase domain becomes activated by binding of the allocrite and provides energy for transmembrane transport. It is thus obvious that there is strong cooperativity between the TM and ATPase domains of the ABC-transporters and they cannot function independently.
- 30 [0004] ATPase domains, homologous to those of the ABC-transporters have recently been identified in DNA repair proteins such as in Rad50, where it was found associated to a DNA binding domain (Hopfner *et al.*, 2000). ATP hydrolysis by the ATPase domain of Rad50 provides the energy required for DNA binding and dissociation. In ABC-transporters, the two ATPase domains or NBD's do not function separately but rather show cooperative ATP hydrolysis, allosterically regulated by ligand binding (Higgins, 1992).
- 35 [0005] The crystal structure recently reported for a dimer of the ATPase domains of the Rad50, protein, shows that conserved motifs, in the ATPase domains form a dimerization interface. This interface holds both the ATP molecules and the two NBD monomers in an optimal conformation for the function of the transporter (Hopfner *et al.*, 2000).

Sequence and structure of the ATPase domains of ABC-transporters.

- 45 [0006] At the sequence level, ABC-ATPases are well conserved, displaying 30 % or more identity between different ABC-transporters. This identity is concentrated in several motifs, which have been used for the recognition of new ABC-transporters. The following sequence elements are typical for ABC-transporter NBD domains: the P-loop or Walker A motif: GAXXGXGKS/TT, where X can be any residue, which is critical for the binding of the beta-phosphate of the ATP nucleotide; the Walker B motif (consensus : HyHyHyHyDE where Hy is a hydrophobic residue). Upstream of the Walker B motif there is a signature motif, SXG where X is mostly G, which is typical for ATPases in ABC-transporters.
- 50 Except for the Walker A motif, the functional significance of the other structural motifs was unclear until the crystal structure of several ABC transporters became available.
- [0007] The crystal structure of HisP from *Salmonella typhimurium* (Hung *et al.*, 1998), showed that the overall shape of the NBD domain is that of an "L", with two arms or lobes (I and II). Lobe I consists primarily of an $\beta/\alpha/\beta$ fold formed by the packing of helix A between two β -sheets consisting of six hydrogen-bonded (3 strands. Lobe II is generated by the packing of three helices against a five-stranded mixed β -sheet. The two lobes are joined into a single folded domain
- 55 by a central beta-sheet II. The nucleotide binding site formed by the Walker A motif (P loop), is located in Lobe I near the interface of both lobes.
- [0008] Several studies have shown that the two NBD domains, NBD1 and NBD2, of ABC-transporters function co-

operatively and that inactivation of one catalytic site completely abolishes ATPase activity and transport function (Holland and Blight, 1999; Higgins, 1992). This can be achieved either by mutations in the Walker A or Walker B site, or by vanadate trapping (Holland and Blight, 1999) of ADP in the catalytic sites. An allosteric regulation of the cooperativity between the two NBD domains is probably a mode of "fine" regulation of these transporters.

[0009] The ABC-transporter family represents a class of proteins with widespread distribution in the human organism sufficing a variety of functions. Moreover, related ABC-transporters are prominent in other eukaryotes and bacteria. A possible way to interfere with the function of these transporters would be to prevent the binding of ATP. Alignment of the nucleotide binding domains of different ABC transporters from mammal and bacterial origin already enabled the identification and localization of the structural elements in the NBD domains of these transporters. Since these elements and especially the P loop are well conserved, problems arise when searching for means of blocking specific ABC-transporters without interfering with the action of other vital members of this protein family. Therefore it is an aim of the present invention to identify molecules and compounds which selectively modulate the activity of ABC transporters.

[0010] It is furthermore an aim of the present invention to provide methods for identifying and inhibiting the dimeric interfaces between the two ATPase domains of ABC-transporters. It is another aim of the invention to provide molecules, compounds and compositions for preventing, treating or alleviating cancer or diseases related to bacterial, fungal and protozoal infections.

SUMMARY OF THE INVENTION

[0011] Three stretches of sequence are crucial for the heterodimeric NBD1-NBD2 structure of ABC-transporters: the residues corresponding to the signature motif, the Walker B motif and the D loop. The present inventors have identified the D-loop as the third important sequence which is conserved amongst ABC transporters. The D-loop immediately follows the Walker B motif and has been named as such by the inventors because they surprisingly found that the last amino acid (Aspartic acid, D) at the end of the conserved loop is very conserved among known ABC-transporter molecules. From several studies supported by extensive molecular modelling of the nucleotide binding domains of HisP, Rad50 and ABC-A1, the present inventors found that this D-loop is also structurally conserved amongst ABC-transporters and forms a central protein-protein dimerization interface (Figure 2). Contacts between the central residues of the D loop may contribute to the optimal dimer interface configuration. A central residue in the D loop could also be involved in the nucleophile attack on the ATP γ phosphate, through hydrogen bonding of an attacking water molecule.

[0012] As described above, the signature motif and Walker A motif, which are part of the dimer interface, belong to the best-conserved elements of the ATPase of ABC-transporters. Until now, the sequence and structure conservation of the D loop had not been described yet for the ABC-transporters. Using the sequence multiple alignment programs, the present inventors identified and analyzed the sequence conservation of these motifs in the ABC-transporters family. Consensus sequences for the D loop in different families of human ABC transporters and in bacterial, protozoal, fungal, and yeast ABC transporters are listed in Tables 1 and 2.

The D-loop as target for inhibition of dimerization of ABC-transporters

[0013] Assembly of different proteins or of different domains within the same protein is a widespread mechanism used for growth and cellular control (Zutshi *et al.*, 1998). Many enzymes, viral proteins, and receptor-ligand interactions are comprised of oligomeric protein complexes (Jones and Thornton, 1996). Assembly of entire proteins or of protein domains are essential elements in allosteric control (Frieden, 1971), signal transduction, viral assembly and replication (Gibson, 1996). The ubiquitous nature of protein-protein interactions in essential cellular processes provides the possibility of developing novel control mechanisms based on inhibition of active protein assemblies. In the past five years, protein-protein interactions in viral enzymes and receptors were inhibited by peptides and small molecules, which led to the development of new antiviral drugs (Brickner and Chmielewski, 1998).

[0014] In the structure of the NBD1-NBD2 heterodimer, only the D-loop provides both efficiency and selectivity for inhibition or enhancement of dimerization of selected transporters. The D-loop residues ensures protein-protein interactions which are specific for sub-families of transporters, whereas dimerization via the signature and Walker A motif involves ATP binding and hydrolysis, a mechanism common to all transporters in the entire ABC family.

DETAILED DESCRIPTION OF THE INVENTION

[0015] The present invention relates to a method for selectively modulating the activity of ABC transporters. One of the possible ways to modulate the activity of ABC transporters is by influencing the dimerization of the nucleotide binding domains.

[0016] Therefore, according to a first embodiment the present invention relates to a method for selectively modulating the activity of ABC transporters by influencing the dimerization of the nucleotide binding domains comprising the use of:

- a) a polypeptide consisting of 6 to 50 amino acids comprising the D loop sequence of an ABC transporter,
- b) a polypeptide consisting of the D loop sequence of an ABC transporter,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the polypeptides of a) or b).

[0017] A list of known human ABC transporter molecules organized by family is provided in Table 1. In Table 2 bacterial, fungal and protozoal ABC transporters are listed. The amino acid sequences of some known examples of ABC transporters are listed in Figure 3.

[0018] The human ABC transporters have been organized in subfamilies, trivially named from ABCA to ABCF transporters and recently reviewed by Klein et al. (1999). Some of these transporters are generally known by their common names, as additionally noted in Table 1 and Figure 3. For instance, the multidrug resistance proteins or P-glycoproteins, now belonging to the ABCB transporters, have been long known as MDR proteins or belonging to the MDR/TAP sub-family.

[0019] In Table 1 and 2, the amino acid sequences of the D loop (in NBD1 and NBD2) are given for each member of the ABC transporter family listed. The D loop sequences are represented in SEQ ID NOs 1 to 43. In cases where only one nucleotide binding domain is present in the protein, for instance when the ABC transporter consists of at least two monomers or subunits, only one D loop sequence is noted in the table(s).

[0020] The expression "ABC transporter(s)", "ABC transporter protein(s)" and "ABC transporter molecule(s)" as used herein are interchangeable.

[0021] As used herein the terms "peptides" and "polypeptides" are interchangeable.

[0022] The term "modulating" relates to increasing, decreasing, inhibiting, abolishing or blocking the activity of selected transporters or groups of transporters within the ABC transporter family. For instance inhibiting the activity results at least in preventing the NBD1-NBD2 hetero-dimerization in such a way that the overall function of the ABC transporter in transporting molecules from one side to the other side of the cellular membrane is affected.

[0023] The expression "selectively modulating the activity" means that only the activity of one specific or at most a few very closely related ABC transporter molecules will be modulated in such a way that it influences the normal activity of said molecule. The "selectivity" resides in the amino acid sequence of the D loop of the nucleotide binding domain (s) of each particular ABC transporter molecule.

[0024] With the expression "D loop" is meant a sequence of 6 to 8 amino acids (ending with an aspartic acid (D)) which immediately follows the highly conserved Walker B motif in the primary structure of the ABC transporters. In each NBD domain of an ABC transporter, a D loop is present at the dimerization interface between the nucleotide binding domains. Interactions between the two D loops or between residues from one D loop and the ATP molecule bound by the second NBD play a key role in the dimerization of NBD's, and as such in the activity of the ABC transporter.

[0025] Therefore, in a more preferred embodiment the invention relates to a method for selectively modulating the activity of ABC transporters by influencing the dimerization of the nucleotide binding domains comprising the use of:

- a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 1 to 43,
- b) a polypeptide consisting of the amino acid sequence as represented in any of SEQ ID NOs 1 to 43 or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the polypeptides of a) or b).

[0026] The expression "influencing the dimerization" can be used for inhibiting or blocking the formation of dimeric interfaces between the two ATPase domains of an ABC-transporter molecule.

[0027] The expression "functional homologue" relates to the corresponding sequences identifiable in other related ABC transporter molecules or relates to the homologous ABC transporter molecule from other organisms. As can be seen from Tables 1 and 2, some of the human ABC transporters have a bacterial or protozoal homologue with an identical D loop sequence. For instance, the D loop sequence of the human ABC transporter B7, belonging to the group of multidrug resistance proteins, is identical to the Pfmdr2 protein of *Plasmodium falciparum*, also known as a multidrug resistance protein. Therefore, it should also be understood that the person skilled in the art from the information herewith provided will know which D-loop sequence and molecules derived therefrom can be used for modulation of specific ABC transporters.

[0028] The expression "peptide mimetic" relates to a molecule that mimics the biological activity of a peptide but is no longer peptidic in chemical structure (Moore, 1996) The term mimetic is sometimes used to describe molecules that are no longer completely peptidic in nature, such as pseudopeptides and peptoids, but a strict definition is a molecule that no longer contains any peptide bonds and has a molecular weight of less than 700 daltons. The production and use of peptide mimetics is known to the one skilled in the art (see for instance Zutshi et al. (1997).

[0029] The term "antisense peptide" is reviewed by Blalock (1990) and by Roubos (1990). In this respect, the molecular recognition theory (Blalock, 1990) states that not only the complementary nucleic acid sequences interact but that, in addition, interacting sites in proteins are composed of complementary amino acid sequences (sense-receptor ligand or sense-antisense peptides). Thus, two peptides derived from complementary nucleic acid sequences in the same reading frame will show a total interchange of their hydrophobic and hydrophilic amino acids when the amino terminus of one is aligned with the carboxy terminus of the other. This inverted hydropathic pattern might allow two such peptides to assume complementary conformations responsible for specific interaction.

[0030] The present inventors found that the D loop is highly conserved in amino acid sequence as well as in structure among all members of ABC transporter family. Nevertheless, said D loop still displays sufficient variability between subfamilies and even between members of a single subfamily to serve as a target for selective interaction with inhibitory peptides or peptide mimetics. In some ABC transporter subfamilies (e.g. ABCB transporters) the sequence of the D loop seems to be conserved in all members of this subfamily for NBD2. In other families, a consensus sequence can be deducted for the D loops (in NBD1 and/or NBD2), as represented in Table 1. Therefore, in some applications it is possible to modulate or block the activity of all members of a specific ABC transporter subfamily using only one polypeptide prototype. Otherwise, in other ABC transporter subfamilies, the activity of specific members can be modulated because sufficient variability in the amino acid sequences of the respective D loops exists. Additionally, in the latter case is it also possible to modulate the activity of all members of said specific ABC transporter subfamily, provided that the consensus D-loop sequence (Tables 1 and 2) is used as a prototype polypeptide.

[0031] The term "prototype polypeptide" should be interpreted as the consensus sequence for the D-loop (e.g. for the ABCG transporter family, the consensus sequence represented in SEQ ID NO 36) on which all possible variants are patterned (e.g. the amino acid sequences represented in SEQ ID NOs 34 and 35).

[0032] "Very closely related" ABC transporter molecules for instance are molecules belonging to the same subfamily.

[0033] Furthermore, it is known that different isoforms exist for particular ABC transporter molecules. The invention thus also relates to possible variants of the D loop between isoforms of the same ABC transporter molecule.

[0034] It should be understood that the possible function and importance of the D loop has not been recognized until the present invention. Also, not all the sequences of ABC transporters are known so that also the consensus sequences for the NBD domain(s) of the transporter(s) may change. Nevertheless it should be recognized that the present invention relates to a general concept and applications of the D loop, which was recognized for the first time by the present inventors. It should therefore, be understood that the invention also relates to all applications and research tools wherein the existence, and the duality between "conserved" and at the same time "variability within the sequence" of the D-loop is used in any possible way already known in the art.

[0035] Furthermore, it should be understood that according to the present invention, molecules comprising the D loop sequences itself can be used or the D loop sequences can be used as a target for modulation or blocking.

[0036] In a preferred embodiment, the invention thus relates to a method for selectively decreasing (or increasing) the activity of an ABC transporter.

[0037] One way of modulating the activity of an ABC transporter is by blocking (or inhibiting) one of the D loops in the dimerization event for instance by a molecule comprising the corresponding amino acid sequence of the second D loop.

[0038] In several diseases associated with the functionality of ABC transporters, inhibition or blocking of the activity of ABC transporters can be beneficial for therapy. Some examples of such ABC transporters are given in bold in Table 1.

[0039] According to the invention, the activity of specific members of the ABC transporter family or groups (e.g. subfamilies) of ABC transporters can be modulated using specific prototype polypeptides as a target.

[0040] Therefore according to a preferred embodiment, the invention relates to a method for selectively modulating, preferably inhibiting or blocking, the activity of an ABC transporter, wherein said ABC transporter belongs to the group of multidrug transporter/P-glycoproteins comprising the use of:

a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NO 1 to 3, more preferably SEQ ID NO 1 and SEQ ID NO 2,

b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NO 1 to 3, or a functional homologue thereof,

c) a peptide mimetic of any of the polypeptides of a) or b), or,

d) an antisense peptide of the polypeptide of a) or b).

[0041] Furthermore, the invention also relates to a method for selectively modulating, preferably inhibiting or blocking, the activity of an ABC transporter wherein said ABC transporter belongs to the group of the multidrug resistance associated proteins comprising the use of:

a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 4 to 15, more preferably SEQ ID NOs 4, 5, 7, 8, 9, 10, 11, 12, 13, 14 or 15,

b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 4 to 15, more preferably SEQ ID NOs 4, 5, 7, 8, 9, 10, 11, 12, 13, 14 or 15, or a functional homologue thereof,

c) a peptide mimetic of any of the polypeptides of a) or b), or,

d) an antisense peptide of the polypeptide of a) or b).

[0042] The ABC transporter molecules belonging to the group of the multidrug transporter/P-glycoproteins and/or multidrug resistance associated proteins are very important in diseases such as cancer.

[0043] The multidrug resistance protein or P-glycoprotein (MDR1 or Pgp1) was the first human ABC protein cloned and is still one of the most intensively studied proteins of the family of the ABCB transporters. This special attention was attracted by the fact that multidrug resistance of cancer cells was found to be caused by this protein.

[0044] Other important candidate ABC transporters belonging to this group are the TAP1 and TAP2 transporters which are associated with antigen processing which activity needs to be suppressed upon transplantation of organs. For the moment, blocking of the activity of said transporters needs the administration of high doses of drugs such as cyclosporine. Reduction in the use of this cyclosporine and avoiding the rejection of the transplant by inhibition of the TAP transporter would increase the success of the transplant.

[0045] Additionally, also the human multidrug resistance associated protein (belonging to the MRP/CFTR or ABCC transporters) confers multidrug resistant phenotype to tumor cells. The majority of non-P-glycoprotein mediated multidrug resistance is due to the over-expression of hMRP1. hMRP1 transports both hydrophobic anticancer agents and anionic (e.g. glutathione) drug conjugates. Its physiological functioning may provide a wide range of cellular xenobiotic resistance. Therefore ABC transporters belonging to this family are especially envisaged in several applications of the present invention.

[0046] Alternatively, the modulation of the activity of an ABC transporter can also result in an improvement of the binding or dimerization of the nucleotide binding domains. Said improvement can be the result of an increase in length of the binding-time period or can be the result of an increase in frequency of dimerization events per time period between the nucleotide binding domains. A positive effect on the dimerization can for instance be achieved by the activity of small peptides or peptide mimetics which directly or indirectly interact with the D loop in a structural (conformational) sense or in an interaction between or with the amino acids constituting the D-loop motif.

[0047] One example of an ABC transporter which is envisaged to benefit from enhancement of activity or of increasing the dimerization event is for instance the CFTR transporter (cystic fibrosis transmembrane conductance regulator). The CFTR transporter is involved with the transport of chloride ions through the membrane. Increasing the activity of said transporter would be beneficial for the treatment of cystic fibrosis patients in which said transporter is defective.

[0048] Also the activity of other ABC transporters can be modulated in a way that increasing the activity is beneficial for therapy. Some examples of such ABC transporters are underlined in Table 1.

[0049] According to a further preferred embodiment the invention relates to a method for selectively modulating, preferably enhancing, the activity of an ABC transporter wherein said ABC transporter is the cystic fibrosis transmembrane conductance regulator (CFTR) comprising the use of:

a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 11 or 12,

b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 11 or 12, or a functional homologue thereof,

c) a peptide mimetic of any of the polypeptides of a) or b), or,

d) an antisense peptide of the peptide of a) or b).

(claims 24-28) Therefore the present invention also relates to the use of a (poly)peptide, antisense peptide or peptide mimetic as defined above or a compound obtainable by one of the compound screening methods described further for treatment of cancer, optionally in combination with chemotherapy. Said (poly)peptides, antisense peptide, peptide mimetic or compound can also be used for treating resistance to drugs in mammals. Said (poly)peptide, antisense peptide, peptide mimetic or compound can also be used for the preparation of a medicine for treating cancer or for preventing, treating or alleviating diseases associated with drug resistance in a mammal.

[0050] ABC transporters are not only important in humans or higher eukaryotes but also bacterial, fungal and protozoal ABC transporters are known wherein a D loop can be recognized as an important structural feature for dimerization and/or functionality and/or activity of said transporter.

[0051] Therefore according to yet another preferred embodiment, the invention relates to a method for selectively modulating the activity of an ABC transporter wherein said ABC transporter is a bacterial transporter comprising the

use of:

- a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 27, 37 to 39,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 27, 37 to 39, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0052] According to yet another preferred embodiment, the invention relates to a method for selectively modulating the activity of an ABC transporter wherein said ABC transporter is a fungal ABC transporter, comprising the use of:

- a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 40 to 42,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 40 to 42, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0053] According to yet another preferred embodiment, the invention relates to a method for selectively modulating the activity of an ABC transporter wherein said ABC transporter is a protozoal ABC transporter, comprising the use of:

- a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NO 2, 8 or 43,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 2, 8 or 43, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0054] Preferably, said bacterial, fungal or protozoal ABC transporter(s) is involved in bacterial, fungal or protozoal infection of a mammal.

[0055] According to a further preferred embodiment, said bacterial, fungal or protozoal ABC transporter is involved in the induction of resistance to antibiotics or other drugs in mammals.

[0056] The activity of bacterial, fungal or protozoal ABC transporters can be explained in a way that they transport antibiotics (or certain classes of antibiotics, or other drugs) which are administered to a human or other mammal in need thereof, to the outside of the bacterial or fungal or protozoal cell wall so that said antibiotics can not exert there anti-bacterial or anti-fungal or anti-protozoal action. Therefore, the (poly)peptides or antisense peptides, or peptide mimetics or compounds that specifically block the ABC transporters in bacteria, fungi and protozoa could potentially be used for the treatment of infections caused by these pathogens. For instance blocking the D loops in the ABC transporters of said pathogens might result in a specific treatment method for bacterial, fungal or protozoal infections. The resulting inhibition of ABC transporter function in these pathogens will cause the death of said pathogen and will be beneficial to the patients. As such these (poly)peptides antisense peptides, peptide mimetics or compounds can be considered as an alternative for antibiotics, antifungicide or anti-protozoal treatment for instance in cases in which a number of organisms have developed already a drug resistance.

[0057] Also co-administration of (poly)peptides or antisense peptides, or peptide mimetic which inhibit or block the activity of bacterial ABC transporters which are involved in such processes or compounds obtainable by one of the compound screening methods described further together with the antibiotic (or drug) would be beneficial to the anti-bacterial action of said antibiotic (or drug).

[0058] Therefore, according to another embodiment the invention also relates to the use of a molecule selected from :

- a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 2, 8, 29 and 37 to 43,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 2, 8, 29 and 37 to 43, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b),

as a anti-bacterial or ant-fungal or anti-protozoal agent.

[0059] It should be noted that SEQ ID NOs 2, 8, and 29 have a homologue in human ABC transporters. However the person skilled in the art perfectly knows which molecules or sequences represented by their SEQ ID NOs to choose when the activity of only bacterial and/or fungal and/or protozoal ABC transporters needs to be modulated. For instance in case an anti-bacterial agent is used, molecules based on SEQ ID NO 43 will be used and not for instance based on SEQ ID NO 2 or 8.

[0060] The recognition of the D-loop as a tool for selectively modulating the activity of ABC transporters can be further exploited in therapy for instance for treatment or for preparation of medicaments.

[0061] Therefore the invention also relates to a method for preventing, treating or alleviating diseases associated with the functionality of a human ABC-transporter comprising the use of:

- a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 1 to 36,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 1 to 36, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0062] Alternatively the invention also relates to a method for the preparation of a medicament for the prevention, treatment or alleviation of diseases associated with the functionality of a human ABC-transporter comprising the use of:

- a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 1 to 36,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 1 to 36, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0063] The invention furthermore relates to a method for preventing, treating or alleviating diseases related with bacterial infections comprising the use of:

- a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0064] Alternatively the invention also relates to a method for the preparation of a medicament for the prevention, treatment or alleviation of diseases associated with bacterial infections comprising the use of:

- a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0065] The invention furthermore relates to a method for preventing, treating or alleviating diseases related with fungal infections comprising the use of:

- a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 40 to 42,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 40 to 42, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0066] Alternatively the invention also relates to a method for the preparation of a medicament for the prevention,

treatment or alleviation of diseases associated with fungal infections comprising the use of:

- a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 40 to 42,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 40 to 42, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0067] The invention furthermore relates to a method for preventing, treating or alleviating diseases related with protozoal infections comprising the use of:

- a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 2, 8, or 43,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 2, 8 or 43, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0068] Alternatively the invention also relates to a method for the preparation of a medicament for the prevention, treatment or alleviation of diseases associated with protozoal infections comprising the use of:

- a) a polypeptide consisting of 6 to 50 amino acids, preferably 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50 amino acids, comprising the amino acid sequence represented in any of SEQ ID NOs 2, 8, or 43,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 2, 8 or 43, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

[0069] The present invention also relates to the use of any of the molecules as defined above or a compound obtainable by any of the compound screening methods described further for preventing, treating or alleviating diseases associated with bacterial, fungal or protozoal infections or for the preparation of a medicament for preventing, treating or alleviating diseases associated with bacterial, fungal or protozoal infections. Furthermore, these molecules or compounds may be used for treating resistance to antibiotics in a mammal or for preparing a medicament for treating resistance to antibiotics or other drugs in a mammal.

[0070] According to another embodiment, the present invention provides methods of identifying compounds which selectively modulate, inhibit, activate or interfere with the properties of ABC transporters. Compounds may carry agonistic or antagonistic properties. The compounds to be screened may be of extracellular, intracellular, biologic or chemical origin.

[0071] Such a screening method may comprise the following steps (a) contacting a compound to be tested with at least one of the polypeptide as defined above under any of a) to d) or with a polypeptide corresponding to the D loop or a nucleotide binding domain of an ABC transporter, (b) detecting a diminution or inhibition of the activity of said ABC transporter, and, (c) identifying said compound.

[0072] Alternatively, in step (b) of the above mentioned method, the effectiveness of said compound can also be investigated by measurement of the ATPase activity in case the compound is contacted with a functional ATPase domain (nucleotide binding domain). Methods to measure ATPase activity are known in the art but are also described further in the examples section.

[0073] The polypeptides according to the invention employed in such a method may be for example in solution or coated on suspended beads. Alternatively, these can be affixed to a solid support, borne on a cell or phage surface or located intracellularly.

[0074] When polypeptide fragments are coated on solid supports, they can be tested for their binding affinity for large numbers of compounds. These can be used in different kinds of high throughput screenings in order to identify compounds having suitable binding affinity to the polypeptides according to the invention. Platform technologies or technologies based on SPR (surface plasmon resonance) can be applied.

[0075] The invention also relates to methods for identifying compounds which selectively bind to or selectively modulate the properties of ABC transporters, which method comprises:

- a) providing a yeast two-hybrid system wherein the nucleotide binding domains NBD1 and NBD2 of an ABC trans-

porter are expressed, or,

b) providing a mammalian expression system wherein the nucleotide binding domains NBD1 and NBD2 of an ABC transporter are expressed, or,

c) providing a bacterial expression system wherein the nucleotide binding domains NBD1 and NBD2 of an ABC transporter are expressed (and/or) or secreted, and,

d) interacting said compound with the complex formed by the expressed polypeptides as defined in any of a) to c),
e) inferring from the interaction between said compound and one of the nucleotide binding domains a modulation of the properties of said ABC transporter, and,

f) identifying said compound.

[0076] Compounds found using this approach and modulating the activity of a selected ABC transporter may additionally be tested on their efficiency to modulate other ABC transporter in order to avoid undesired cross-activity of said compounds on non selected ABC transporters.

[0077] Alternatively additional tests can be performed to test the influence of the compound onto protein stability, post-translational modification, precursor processing and protein translocation. All these aspects influence the concentration and/or activity of corresponding proteins and consequently influence the effect of these onto the metabolism of the cell. Also here, medium or low throughput systems can be used to confirm results obtained by the high throughput assays.

[0078] Compounds obtainable by one of the methods described above or the use of said compounds as a medicament also form part of the invention.

[0079] The invention also relates to an isolated nucleic acid encoding at least one of the polypeptides defined above in a) to d) comprising an ABC transporter D loop represented in any of SEQ ID NOs 1 to 43.

[0080] The invention further relates to a polypeptide encodable by and isolated nucleic acid as defined above.

[0081] The invention also relates to a composition, preferably a pharmaceutical composition, comprising at least one polypeptides of the invention and to the use of said polypeptide or of the composition comprising said polypeptide as a medicament.

[0082] The invention also relates to a cellular host for use in a method described above, said cellular host transformed with a nucleic acid encoding at least one nucleotide binding domain of an ABC transporter protein or a nucleic acid comprising a nucleic acid as described above, said nucleic acid in an expressible format.

[0083] The cellular hosts used in the invention can be from bacterial, fungal, vegetal or mammalian origin. There are numerous vectors, expression systems and methods known in the art to allow the skilled in the art for transforming, transfecting or infecting the desired host cell with the desired nucleic acid in order to obtain desired expression of any of the polypeptides of the invention.

[0084] The invention, now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention and are not intended to limit the invention. All of the references mentioned herein are incorporated by reference.

BRIEF DESCRIPTION OF TABLES AND FIGURES

[0085]

Figure 1. Schematic representation of the ABC transporters.

Figure 2. Schematic presentation of positioning of the ATP-binding site and the dimerization-interface in the ABC transporter molecule.

Figure 3. Amino acid sequences of human, bacterial, protozoal and fungal transporters: examples. The underlined sequences refer to the D loops in these sequences. The names of the sequences given after each ">" refer to the names given in Tables 1 and 3.

Table 1. Sequences of the D loops in different human ABC transporters, and derived consensus sequence for each family. Marked in ***bold** are the candidate transporters for inhibition of activity. Marked underlined are the candidate transporters for increase of activity.

Table 2: Sequences of the D loops in different ABC transporters from bacteria fungi and protozoa. All transporters are candidate transporters for inhibition.

TABLE 1 : D loops in human ABC transporter families.

ABCA TRANSPORTERS

NAME	COMMON NAME	SEQUENCE	SEQ ID NO
A1	ABC1	PTAGVD PTTGMD	SEQ ID NO 16 SEQ ID NO 17
A2	ABC2	PTAGVD PTTGMD	
A3	ABC-C	PTSGMD PSTGMD	SEQ ID NO 18 SEQ ID NO 19
A4	ABC-R	PTSGVD PTTGMD	SEQ ID NO 20
A7	ABCX	PTAGVD PTTGMD	
A8	ACGA8	PTAGLD PSTGMD	SEQ ID NO 21

CONSENSUS

NBD1 P T A G (V/L) D (SEQ ID NO 22) or P T S G (M/V) D (SEQ ID NO 23)
 NBD2 P (T/S) T G M D (SEQ ID NO 24)

ABCB TRANSPORTERS –(MDR/TAP)

NAME	COMMON NAME	SEQUENCE	SEQ ID NO
*B1	MDR1 or P GLYCOPROT	ATSALD ATSALD	SEQ ID NO 1
B2	TAP1	ATSALD	
B3	TAP2	ATSALD	
*B4	MDR2/3	ATSALD ATSALD	
B6		ATSALD	
B7		ATSSLD	SEQ ID NO 2
B8		ATSALD	
B9		ATSALD	
B10		ATSALD	
*B11	SPGP	ATSALD ATSALD	

CONSENSUS :

NBD1 A T S (A/S) L D (SEQ ID NO 3)
 NBD2 A T S A L D

TABLE 1 - Continued

ABCC TRANSPORTERS (MRP/SUR/CFTR)

NAME	COMMON NAME	SEQUENCE	SEQ ID NO
*C1	MRP1 (Multidrug resistance associated protein)	PLSAVD ATAAVD	SEQ ID NO 4 SEQ ID NO 5
C2	MRP2	PLSAVD ATAAVD	
C3	MRP3	PLSAVD ATAAID	SEQ ID NO 6
*C4	MRP4	PLSAVD ATANVD	SEQ ID NO 7
*C5	MRP5	PLSALD ATAAMD	SEQ ID NO 8 SEQ ID NO 9
*C6	MRP6	PLAALD ATAAVD	SEQ ID NO 10
C7	CFTR	PFGYLD PSAHL	SEQ ID NO 11 SEQ ID NO 12
*C8	SUR1 (Sulfonurea receptor)	PFSALD ATASID	SEQ ID NO 13 SEQ ID NO 14
*C9	SUR2	PFSALD ATASID	
C10		PLAAVD ATASVD	SEQ ID NO 15

ABCD TRANSPORTERS

NAME	COMMON NAME	SEQUENCE	SEQ ID NO
D1	ALDP	CTSAVSID	SEQ ID NO 25
D2	ALDR	CTSAVSID	
D3	PXMP1	CTSAVSVD	SEQ ID NO 26
D4	PXMP1L	ATSALTEE	SEQ ID NO 27

TABLE 1 - Continued

ABCE TRANSPORTER

NAME	COMMON NAME	SEQUENCE	SEQ ID NO
E1	RNASELI	PSAYLD	SEQ ID NO 28

ABCF TRANSPORTER

NAME	COMMON NAME	SEQUENCE	SEQ ID NO
F1	MDR	PTNHLD PTNNLD	SEQ ID NO 29 SEQ ID NO 30
F2		PTNHLD PTNHLD	
F3		PTNMLD PTNHLD	SEQ ID NO 31

CONSENSUS

NBD1 P T N (H/M) L D (SEQ ID NO 32)

NBD2 P T N (N/H) L D (SEQ ID NO 33)

ABCG TRANSPORTERS

NAME	COMMON NAME	SEQUENCE	SEQ ID NO
G1	ABC8White	PTSGLD	SEQ ID NO 34
*G2	BCRP1	PTTGLD	SEQ ID NO 35
G5		PTTGLD	
G8		PTSGLD	

CONSENSUS P T (T/S) G L D (SEQ ID NO 36)

TABLE 2: D LOOPS IN BACTERIAL, FUNGAL AND PROTOZOAL ABC TRANSPORTERS

BACTERIA

PROTEIN	SEQUENCE	FUNCTION	SPECIES	SEQ ID NO
LmrA	ATASLD	Lincomycin resistance	<i>Streptomyces lincolnensis</i>	SEQ ID NO 37
DrrA	ADQLAD	daunorubicin resistance	<i>Lactococcus lactis</i>	SEQ ID NO 38
OLEB	PTNHLD	oleandomycin resistance	<i>Streptomyces paucatus</i>	SEQ ID NO 39
	PTNHLS		<i>Streptomyces coelicolor</i>	SEQ ID NO 39

FUNGI

PROTEIN	SEQUENCE	SPECIES	SEQ ID NO
Bfr1	STRGLD	<i>Schizosaccharomyces pombe</i>	SEQ ID NO 40
	PTSGLD		SEQ ID NO 41
Cdr1	ATRGLD	<i>Candida albicans</i>	SEQ ID NO 42
	PTSGLD		
Cdr2	ATRGLD	<i>Candida albicans</i>	
	PTSGLD		
Pdr5p	ATRGLD	<i>Saccharomyces cerevisiae</i>	
	PTSGLD		
Snq2p	ATRGLD	<i>Saccharomyces cerevisiae</i>	
	PTSGLD		

PROTOZOA

PROTEIN	SEQUENCE	FUNCTION	SPECIES	SEQ ID NO
Pfmdr2	ATSSLD	Multidrug resistance protein 2	<i>Plasmodium falciparum</i>	
MDR-PLAFA	ATSSLD	chloroquine, mefloquine	<i>Plasmodium falciparum</i>	
	ATSSLD	halofantidine resistance	Malaria	
DVLNS ?	PLSALD	methotrexate resistance	<i>Leishmania tarentolae</i>	SEQ ID NO 43
	ATANID			

EXAMPLES

Example 15 **1. Molecular modeling of the ATP binding cassette (ABC) domain.**

[0086] The ABC-1 transporter contains two different nucleotide binding domains (NBD1 and NBD2), involved in the hydrolysis of ATP. The first structure of a nucleotide binding domain of an ABC transporter that has been determined by crystallization and X-ray diffraction analysis is the ATP binding cassette HisP of the *Salmonella typhimurium* histidine permease. There is significant sequence homology between HisP and both nucleotide binding domains of ABCA1, and the major structure elements of HisP are conserved. The two nucleotide binding domains (NBD) of ABCA1 can therefore be modeled, based on the coordinates of the crystal structure of HisP.

[0087] The structure of the ATPase domain of the Rad50 protein, determined by crystallisation and X-ray diffraction is very similar to the HisP structure. In the presence of a non-hydrolyzable ATP analogue, the Rad50 ATPase crystallised as a dimer. This dimeric structure forms a reliable template to model dimerization of two HisP monomers and to model the putative dimeric configuration of NBD1 and NBD2 of ABCA1 and of other related ABC transporters. From these models, the actual dimer interface is be studied in closer detail and mutations impairing dimerization of the nucleotide binding domains are proposed.

20 **2. Homology modeling**

[0088] Sequence homology and alignments between the NBD domains of different human and bacterial ABC transporters were analyzed using BLAST, CLUSTALX and DIALIGN. Secondary structure prediction were carried out using the PHD, JPRED softwares. 3D homology calculations and model building were performed using MSI Insight 2000 software on a Silicon Graphics 02 computer, combined with SCWRL. Models are checked using Procheck, Prosa II, WHATIFF and 3D- profiles.

[0089] The built models for the two ABCA1 ATP nucleotide binding domains allow identification and characterization of the ATP binding site and dimerization site, and the design of ABCA1 mutants that lose either ATP binding, or ATPase activity or without significant structure perturbations. The models also help identify residues involved in protein-protein interactions between NBD1 and NBD2 of ABCA1.

Example 235 **1. Cloning of the nucleotide binding domains and transformation of *E. coli*.**

[0090] The ABCA1 cDNA is cloned in the pcDNA3.1 plasmid under control of the T7 promotor. Because no unique restriction sites are present close to the boundaries of the NBD domains the individual nucleotide binding domains are generated by direct PCR of these regions (Taq polymerase). These PCR products are introduced in the pTrcHis TOPO plasmid (Invitrogen) that introduces directly a 6X His tail at the N-terminus and is under control of a Trc promotor. After purification, the His tag can be removed by treatment with enterokinase. Point mutations in these domains are introduced by the Quickchange mutagenesis kit (Stratagene).

[0091] Transformation of TOP10 Oneshot competent *E. coli* is performed by 'heat-shock' at 42°C during 30 seconds. The transformed *E. coli* are grown overnight at 37°C in Luria-Bertani (LB) medium. Plasmid DNA is isolated using the MiniPrep kit (Invitrogen) and checked by sequencing.

45 **2. Expression and purification of the nucleotide binding domains**

[0092] The optimal conditions for growth and expression are determined using standard procedures. Once the optimal conditions for expression are determined, a larger scale culture is prepared.

[0093] The expressed NBD proteins are isolated from the *E. coli* after lysis of the bacteria by sonication. Nucleic acids are precipitated with streptomycin sulphate (10%) and removed by centrifugation. The supernatant containing the NBD-His proteins is purified by affinity chromatography using a Ni²⁺-agarose matrix (ProBond). The presence of the NBD protein in the eluate is verified by SDS-PAGE and Coomassie staining. The N-terminal 6xHis tag is removed by treatment with enterokinase Max.

Example 3: ATP binding and hydrolysis after incubation with the NBD's.**1. ATP binding using a fluorescent labeled ATP-analogue: 2'-O-(2,4,6-trinitrophenyl) adenosine 5'-trifosfaat (TNP-ATP).**

[0094] Unbound TNP nucleotides (Molecular Probes) dissolved in water display no fluorescence emission but become fluorescent once bound to nucleotide binding proteins such as ATPases. 150 µg/ml NBD1 are incubated at 25°C with 2 µM TNP-ATP, 0,8 mM EDTA in a 40 mM Tris-HCl buffer (pH 7,4). Fluorescence emission is measured on an Aminco Bowman fluorescence spectrophotometer (excitation wavelength 405 nm, emission 546 nm). The concentration of the TNP-ATP is determined spectrophotometrically at 408 nm using an extinction coefficient of $2,64 \times 10^4 \text{ M}^{-1}\text{cm}^{-1}$.

2. ATP hydrolysis measured using radiolabeled ATP.

[0095] ATP-ase activity is measured as described by Gradia et al. (1997). The NBD proteins ($\pm 100 \text{ nM}$) are incubated in 40 mM HEPES (pH 7,8), 75 mM NaCl, 10 mM MgCl_2 , 1,75 mM DTT, 0,075 mM EDTA, 15% glycerol, 75 µg/ml acetylated BSA (Promega) and 500 mM ATP supplemented with 1 µCi $\gamma\text{-}^{32}\text{P}$ -ATP. This mixture is incubated during 30 min at 37°C and stopped by adding an excess 10% activated charcoal dissolved in 1 mM EDTA. After removal of the charcoal by centrifugation the ^{32}P -orthophosphate is measured by liquid scintillation counting.

3. ATP hydrolysis measured by following the amount of anorganic phosphate formed using a colorimetric assay.

[0096] The EnzChek phosphate assay kit (Molecular Probes) permits the measurement of ATPase activity measurements. During the enzymatic reaction the substrate MESG (2-amino-6-mercapto-7-methylpurineribonucleoside absorbance 330 nm) is converted, in the presence of inorganic phosphate and purine nucleoside phosphorylase (PNP), to ribose-1-phosphate and 2-amino-6mercapto-7-methylpurine which absorbs at 355 nm. The change in the absorption maximum of the MESG and the methylpurine allows quantification of the inorganic phosphate consumed in the reaction mixture. The NBD proteins are incubated in 50 mM HEPES (pH 7.3) containing 150 mM KCl, 10 mM MgCl_2 , 1 mM DTT and 400 µM ATP. The reaction mixture is then mixed with the substrates and enzymes contained in the kit according to the instructions of the manufacturer.

Example 4: Interaction between NBD1 and NBD2**1. Gel-filtration**

[0097] 50 µg NBD1 and 50 µg NBD2 in 50 mM Tris pH 7,4 buffer containing 1 mM EDTA, 10 mM MgCl_2 are incubated in the presence or absence of 5 mM ATP. This mixture is analyzed on a Superdex 200 column (Pharmacia) in an FPLC system (same buffer). The eluted proteins are followed at 280 nm and the elution volume is used for the calculation of the molecular weight, using a calibration curve with protein standards.

2. Dynamic lightscattering to determine the size of the dimer-monomer

[0098] These measurements are performed on a DLS-700 photometer (Otsuka). Samples (NBD1 or NBD 2 only or NBD1/NBD2 mixtures) are prepared at a concentration of $\pm 1 \text{ mg/ml}$ in a 0.1 M Tris-HCl (pH 7.5) containing 200 mM NaCl and 10 mM MgCl_2 at 22°C. ATP at concentrations up to 10 mM can be added to the mixture to promote dimerization. Scattering intensity is recorded for 5-10 min.

3. Native gradient polyacrylamide gelelectroforese.

[0099] 4-20% Tris-HCl Ready gels (Biorad) are run in 90 mM Tris-HCl, 2 mM EDTA, 30 mM NaN_3 en 80 mM boric acid. 15 µg NBD protein (either NBD1, NBD2 or the mixture) are incubated with 0,2 µM ATP. After equilibration of the samples they are run on the gel for 1 hour at 70V, and then overnight (with cooling) at 120 V. The gels are stained with Coomassie Brilliant Blue and destained in 40% methanol/10% acetic acid

4. Solid phase assay for evaluating of the binding of NBD1 and NBD2

[0100] The NBD1 protein is coated at the surface of polystyrene microtiterplates and the excess protein is washed

(PBS (pH 7.5- Tween 20 0.1%) and remaining binding sites on the plate are blocked with casein (0.1% in PBS pH 7.5). The NBD2 protein is added in increasing amounts to the coated protein in the presence or absence of ATP in a PBS-0.1% casein buffer. Bound NBD2 (containing the N-terminal His tag) is detected using an anti-His monoclonal antibody () followed by incubation with an anti-mouse IgG peroxidase labeled antibody. Alternatively NBD2 directly labelled with peroxidase or alkaline phosphatase can be used for detection. The amount of bound enzyme is revealed using chromogenic or fluorometric substrates. This type of assay can be adapted for evaluation in plasmon resonance technique (BIAcore system (Amersham)), where either NBD1 or NBD2 is adsorbed on the surface.

5. Inhibition of dimerization using competitor peptides or peptides or small compounds blocking the D-loop

[0101] The assays mentioned above are performed in the presence of synthetic peptides corresponding to the D-loop (competition) or in the presence of peptides or small compounds that sterically block access to the D-loop (cf. modeling). Peptides are prepared using standard protocols and are added to the incubation mixtures at varying concentrations.

6. Evaluation of mutant NBD proteins

[0102] As described in the modeling section mutations in the NBD proteins will be proposed. Special emphasis will be given to the mutations aimed at influencing the dimer interface properties of these proteins. The ATPase activity and dimerization properties of the mutant NBDs will be tested as described above.

REFERENCES

[0103]

Bodzioch M, Orso E, Klucken J, Langmann T, Bottcher A, Diederich W, Drobnik W, Barlage S, Buchler C, Porsch-Ozcurumez M, Kaminski WE, Hahmann HW, Oette K, Rothe G, Aslanidis C, Lackner KJ, Schmitz G: The gene encoding ATP-binding cassette transporter 1 is mutated in Tangier disease. *Nat.Genet.* 22:347,1999.

Borst P, Zelcer N, van Helvoort A: ABC transporters in lipid transport. *Biochim.Biophys.Acta* 2000.Jun.26.;1486.(1.):128.-44. 1486:128.

Blalock, JE: Complementarity of peptides specified by 'sense' and 'antisense' strands of DNA. *Trends Biotechnol.* 8(6): 140-144, 1990.

Brickner M, Chmielewski J: Inhibiting the dimeric restriction endonuclease EcoRI using interfacial helical peptides. *Chem.Biol.* 5:339, 1998.

Brooks-Wilson A, Marcil M, Clee SM, Zhang LH, Roomp K, van Dam M, Yu L, Brewer C, Collins JA, Molhuizen HO, Loubser O, Ouelette BF, Fichter K, Ashbourne-Excoffon KJ, Sensen CW, Scherer S, Mott S, Denis M, Martindale D, Frohlich J, Morgan K, Koop B, Pimstone S, Kastelein JJ, Hayden MR: Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency *Nat.Genet.* 22:336, 1999.

Frieden C: Protein-protein interaction and enzymatic activity. *Annu.Rev.Biochem.* 40:653, 1971.

Gibson W: Structure and assembly of the virion. *Intervirology* 39:389, 1996.

Gradia, S., Acharya, S., Fishel, R. The human mismatch recognition complex hMSH2-hMSH6 functions as a novel molecular switch. *Cell*, 91: 995,1997.

Holland IB, Blight MA: ABC-ATPases, adaptable energy generators fuelling transmembrane movement of a variety of molecules in organisms from bacteria to humans. *J.Mol.Biol.* 293:381, 1999.

Higgins CF: ABC transporters: from microorganisms to man. *Annu.Rev.Cell Biol.* 8:67, 1992.

Hipfner DR, Deeley RG, Cole SP: Structural, mechanistic and clinical aspects of MRP1. *Biochim.Biophys.Acta* 1461:359, 1999.

EP 1 217 066 A1

Hopfner KP, Karcher A, Shin DS, Craig L, Arthur LM, Carney JP, Tainer JA: Structural biology of Rad50 ATPase: ATP-driven conformational control in DNA double-strand break repair and the ABC-ATPase superfamily. *Cell* 2000.Jun.23.;101.(7.):789-800. 101:789.

5 Hung LW, Wang IX, Nikaido K, Liu PQ, Ames GF, Kim SH: Crystal structure of the ATP-binding subunit of an ABC transporter. *Nature* 396:703, 1998.

Jones S, Thornton JM: Principles of protein-protein interactions. *Proc.Natl.Acad.Sci.U.S.A.* 93:13, 1996.

10 Klein I, Sarkadi B, Varad A. An inventory of human ABC proteins. *Biochim Biophys Acta* 1461(2): 237-262, 1999.

Roubos E. Sense-antisense complementarity of hormone-receptor interaction sites. *Trends Biotechnol* 8(10): 279-281, 1990.

15 Rust S, Rosier M, Funke H, Real J, Amoura Z, Piette JC, Deleuze JF, Brewer HB, Duverger N, Deneffe P, Assmann G: Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1 *Nat.Genet.* 22:352, 1999

Sheppard DN, Welsh MJ: Structure and function of the CFTR chloride channel. *Physiol.Rev.* 79:S23, 1999

20

Zielenski J, Tsui LC: Cystic fibrosis: genotypic and phenotypic variations. *Annu.Rev.Genet.* 29:777, 1995

Zutshi R, Franciskovich J, Shultz M, Schweitzer B, Bishop P, Wilson M, Chmielewski J. Targeting the dimerization interface of HIV-1 protease: inhibition with Cross-linked Interfacial peptides. *J AM Chem Soc*, 119: 4841-4845, 1997

25

Zutshi R, Brickner M, Chmielewski J: Inhibiting the assembly of protein-protein interfaces. *Curr.Opin.Chem.Biol.* 2:62, 1998

30

35

40

45

50

55

EP 1 217 066 A1

SEQUENCE LISTING

5 <110> UNIVERSITEIT GENT

<120> Modulation of ATP-binding cassette transporter activity

10 <130> UG-013-EP

<140> EP 00870316.7

<141> 2000-12-21

15 <160> 92

<170> PatentIn Ver. 2.1

20 <210> 1

<211> 6

<212> PRT

<213> Homo sapiens

25 <400> 1

Ala Thr Ser Ala Leu Asp

1 5

30 <210> 2

<211> 6

<212> PRT

35 <213> Homo sapiens

<400> 2

Ala Thr Ser Ser Leu Asp

40 1 5

45 <210> 3

<211> 6

<212> PRT

<213> Homo sapiens

50 <220>

<221> VARIANT

<222> (4)

<223> Xaa = Ala or Ser

55 <400> 3

EP 1 217 066 A1

5
Ala Thr Ser Xaa Leu Asp
1 5

10
<210> 4
<211> 6
<212> PRT
<213> Homo sapiens

15
<400> 4
Pro Leu Ser Ala Val Asp
1 5

20
<210> 5
<211> 6
<212> PRT
<213> Homo sapiens

25
<400> 5
Ala Thr Ala Ala Val Asp
1 5

30
<210> 6
<211> 6
<212> PRT
<213> Homo sapiens

35
<400> 6
Ala Thr Ala Ala Ile Asp
1 5

40
<210> 7
<211> 6
<212> PRT
<213> Homo sapiens

45
<400> 7
Ala Thr Ala Asn Val Asp
1 5

50
<210> 7
<211> 6
<212> PRT
<213> Homo sapiens

55
<400> 7
Ala Thr Ala Asn Val Asp
1 5

EP 1 217 066 A1

	<210> 8
	<211> 6
5	<212> PRT
	<213> Homo sapiens
	<400> 8
10	Pro Leu Ser Ala Leu Asp
	1 5
15	<210> 9
	<211> 6
	<212> PRT
	<213> Homo sapiens
20	<400> 9
	Ala Thr Ala Ala Met Asp
	1 5
25	<210> 10
	<211> 6
30	<212> PRT
	<213> Homo sapiens
	<400> 10
35	Pro Leu Ala Ala Leu Asp
	1 5
40	<210> 11
	<211> 6
	<212> PRT
	<213> Homo sapiens
45	<400> 11
	Pro Phe Gly Tyr Leu Asp
	1 5
50	<210> 12
	<211> 6
55	<212> PRT

EP 1 217 066 A1

<213> Homo sapiens

<400> 12

Pro Ser Ala His Leu Asp
1 5

<210> 13

<211> 6

<212> PRT

<213> Homo sapiens

<400> 13

Pro Phe Ser Ala Leu Asp
1 5

<210> 14

<211> 6

<212> PRT

<213> Homo sapiens

<400> 14

Ala Thr Ala Ser Ile Asp
1 5

<210> 15

<211> 6

<212> PRT

<213> Homo sapiens

<400> 15

Pro Leu Ala Ala Val Asp
1 5

<210> 16

<211> 6

<212> PRT

<213> Homo sapiens

<400> 16

Pro Thr Ala Gly Val Asp

EP 1 217 066 A1

	1	5
5		
	<210> 17	
	<211> 6	
10	<212> PRT	
	<213> Homo sapiens	
	<400> 17	
15	Pro Thr Thr Gly Met Asp	
	1	5
20	<210> 18	
	<211> 6	
	<212> PRT	
	<213> Homo sapiens	
25	<400> 18	
	Pro Thr Ser Gly Met Asp	
	1	5
30		
	<210> 19	
	<211> 6	
35	<212> PRT	
	<213> Homo sapiens	
	<400> 19	
40	Pro Ser Thr Gly Met Asp	
	1	5
45	<210> 20	
	<211> 6	
	<212> PRT	
	<213> Homo sapiens	
50	<400> 20	
	Pro Thr Ser Gly Val Asp	
	1	5
55		

EP 1 217 066 A1

5
 <210> 21
 <211> 6
 <212> PRT
 <213> Homo sapiens

 <400> 21
Pro Thr Ala Gly Leu Asp
1 5

15
 <210> 22
 <211> 6
 <212> PRT
 <213> Homo sapiens

20
 <220>
 <221> VARIANT
 <222> (5)
 <223> Xaa = Val or Leu

25
 <400> 22
Pro Thr Ala Gly Xaa Asp
1 5

30

 <210> 23
 <211> 6
 <212> PRT
 <213> Homo sapiens

35
 <220>
 <221> VARIANT
 <222> (5)
 <223> Xaa = Met or Val

40
 <400> 23
Pro Thr Ser Gly Xaa Asp
1 5

45

50
 <210> 24
 <211> 6
 <212> PRT
55
 <213> Homo sapiens

EP 1 217 066 A1

5 <220>
 <221> VARIANT
 <222> (2)
 <223> Xaa = Thr or Ser

 <400> 24
 10 Pro Xaa Thr Gly Met Asp
 1 5

 15 <210> 25
 <211> 8
 <212> PRT
 <213> Homo sapiens

 20 <400> 25
 Cys Thr Ser Ala Val Ser Ile Asp
 1 5

 25

 30 <210> 26
 <211> 8
 <212> PRT
 <213> Homo sapiens

 35 <400> 26
 Cys Thr Ser Ala Val Ser Val Asp
 1 5

 40 <210> 27
 <211> 8
 <212> PRT
 <213> Homo sapiens

 45 <400> 27
 Ala Thr Ser Ala Leu Thr Glu Glu
 1 5

 50

 55 <210> 28
 <211> 6
 <212> PRT
 <213> Homo sapiens

EP 1 217 066 A1

5 <400> 28
 Pro Ser Ala Tyr Leu Asp
 1 5

10 <210> 29
 <211> 6
 <212> PRT
 <213> Homo sapiens

15 <400> 29
 Pro Thr Asn His Leu Asp
 1 5

20

25 <210> 30
 <211> 6
 <212> PRT
 <213> Homo sapiens

30 <400> 30
 Pro Thr Asn Asn Leu Asp
 1 5

35 <210> 31
 <211> 6
 <212> PRT
 <213> Homo sapiens

40 <400> 31
 Pro Thr Asn Met Leu Asp
 1 5

45

50 <210> 32
 <211> 6
 <212> PRT
 <213> Homo sapiens

55 <220>
 <221> VARIANT
 <222> (4)

EP 1 217 066 A1

<223> Xaa = His or Met

5

<400> 32

Pro Thr Asn Xaa Leu Asp

1 5

10

<210> 33

<211> 6

<212> PRT

15

<213> Homo sapiens

<220>

<221> VARIANT

<222> (4)

20

<223> Xaa = Asn or His

<400> 33

Pro Thr Asn Xaa Leu Asp

25

1 5

30

<210> 34

<211> 6

<212> PRT

<213> Homo sapiens

35

<400> 34

Pro Thr Ser Gly Leu Asp

1 5

40

<210> 35

<211> 6

<212> PRT

45

<213> Homo sapiens

<400> 35

Pro Thr Thr Gly Leu Asp

50

1 5

55

<210> 36

<211> 6

EP 1 217 066 A1

<212> PRT
<213> Homo sapiens

5

<220>
<221> VARIANT
<222> (3)
<223> Xaa = Thr or Ser

10

<400> 36
Pro Thr Xaa Gly Leu Asp
1 5

15

<210> 37
<211> 6
<212> PRT
<213> Streptomyces lincolnensis

20

<400> 37
Ala Thr Ala Ser Leu Asp
1 5

25

30

<210> 38
<211> 6
<212> PRT
<213> Streptomyces peucetius

35

<400> 38
Ala Asp Gln Leu Ala Asp
1 5

40

<210> 39
<211> 6
<212> PRT
<213> Streptomyces coelicolor

45

<400> 39
Pro Thr Asn His Leu Ser
1 5

50

55

<210> 40

EP 1 217 066 A1

5
 <211> 6
 <212> PRT
 <213> Schizosaccharomyces pombe

10
 <400> 40
 Ser Thr Arg Gly Leu Asp
 1 5

15
 <210> 41
 <211> 6
 <212> PRT
 <213> Schizosaccharomyces pombe

20
 <400> 41
 Pro Thr Ser Gly Leu Asp
 1 5

25
 <210> 42
 <211> 6
 <212> PRT

30
 <213> Candida albicans

35
 <400> 42
 Ala Thr Arg Gly Leu Asp
 1 5

40
 <210> 43
 <211> 6
 <212> PRT

45
 <213> Leishmania tarentolae

50
 <400> 43
 Ala Thr Ala Asn Ile Asp
 1 5

55
 <210> 44
 <211> 2261
 <212> PRT
 <213> Homo sapiens

EP 1 217 066 A1

<400> 44

	Met	Ala	Cys	Trp	Pro	Gln	Leu	Arg	Leu	Leu	Leu	Trp	Lys	Asn	Leu	Thr
	1				5					10					15	
5																
	Phe	Arg	Arg	Arg	Gln	Thr	Cys	Gln	Leu	Leu	Leu	Glu	Val	Ala	Trp	Pro
				20					25					30		
10	Leu	Phe	Ile	Phe	Leu	Ile	Leu	Ile	Ser	Val	Arg	Leu	Ser	Tyr	Pro	Pro
		35					40						45			
	Tyr	Glu	Gln	His	Glu	Cys	His	Phe	Pro	Asn	Lys	Ala	Met	Pro	Ser	Ala
15		50					55					60				
	Gly	Thr	Leu	Pro	Trp	Val	Gln	Gly	Ile	Ile	Cys	Asn	Ala	Asn	Asn	Pro
	65					70					75					80
20	Cys	Phe	Arg	Tyr	Pro	Thr	Pro	Gly	Glu	Ala	Pro	Gly	Val	Val	Gly	Asn
					85					90					95	
	Phe	Asn	Lys	Ser	Ile	Val	Ala	Arg	Leu	Phe	Ser	Asp	Ala	Arg	Arg	Leu
25				100					105					110		
	Leu	Leu	Tyr	Ser	Gln	Lys	Asp	Thr	Ser	Met	Lys	Asp	Met	Arg	Lys	Val
			115					120					125			
30	Leu	Arg	Thr	Leu	Gln	Gln	Ile	Lys	Lys	Ser	Ser	Ser	Asn	Leu	Lys	Leu
		130					135						140			
	Gln	Asp	Phe	Leu	Val	Asp	Asn	Glu	Thr	Phe	Ser	Gly	Phe	Leu	Tyr	His
35	145					150					155					160
	Asn	Leu	Ser	Leu	Pro	Lys	Ser	Thr	Val	Asp	Lys	Met	Leu	Arg	Ala	Asp
					165					170					175	
40																
	Val	Ile	Leu	His	Lys	Val	Phe	Leu	Gln	Gly	Tyr	Gln	Leu	His	Leu	Thr
				180					185					190		
	Ser	Leu	Cys	Asn	Gly	Ser	Lys	Ser	Glu	Glu	Met	Ile	Gln	Leu	Gly	Asp
45			195				200						205			
	Gln	Glu	Val	Ser	Glu	Leu	Cys	Gly	Leu	Pro	Arg	Glu	Lys	Leu	Ala	Ala
		210					215					220				
50																
	Ala	Glu	Arg	Val	Leu	Arg	Ser	Asn	Met	Asp	Ile	Leu	Lys	Pro	Ile	Leu
	225					230					235					240
55	Arg	Thr	Leu	Asn	Ser	Thr	Ser	Pro	Phe	Pro	Ser	Lys	Glu	Leu	Ala	Glu
				245						250					255	

EP 1 217 066 A1

5	Ala Thr Lys Thr Leu Leu His Ser Leu Gly Thr Leu Ala Gln Glu Leu	260	265	270
	Phe Ser Met Arg Ser Trp Ser Asp Met Arg Gln Glu Val Met Phe Leu	275	280	285
10	Thr Asn Val Asn Ser Ser Ser Ser Ser Thr Gln Ile Tyr Gln Ala Val	290	295	300
15	Ser Arg Ile Val Cys Gly His Pro Glu Gly Gly Gly Leu Lys Ile Lys	305	310	315
	Ser Leu Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Leu Phe Gly Gly	325	330	335
20	Asn Gly Thr Glu Glu Asp Ala Glu Thr Phe Tyr Asp Asn Ser Thr Thr	340	345	350
25	Pro Tyr Cys Asn Asp Leu Met Lys Asn Leu Glu Ser Ser Pro Leu Ser	355	360	365
	Arg Ile Ile Trp Lys Ala Leu Lys Pro Leu Leu Val Gly Lys Ile Leu	370	375	380
30	Tyr Thr Pro Asp Thr Pro Ala Thr Arg Gln Val Met Ala Glu Val Asn	385	390	395
35	Lys Thr Phe Gln Glu Leu Ala Val Phe His Asp Leu Glu Gly Met Trp	405	410	415
	Glu Glu Leu Ser Pro Lys Ile Trp Thr Phe Met Glu Asn Ser Gln Glu	420	425	430
40	Met Asp Leu Val Arg Met Leu Leu Asp Ser Arg Asp Asn Asp His Phe	435	440	445
45	Trp Glu Gln Gln Leu Asp Gly Leu Asp Trp Thr Ala Gln Asp Ile Val	450	455	460
	Ala Phe Leu Ala Lys His Pro Glu Asp Val Gln Ser Ser Asn Gly Ser	465	470	475
50	Val Tyr Thr Trp Arg Glu Ala Phe Asn Glu Thr Asn Gln Ala Ile Arg	485	490	495
55	Thr Ile Ser Arg Phe Met Glu Cys Val Asn Leu Asn Lys Leu Glu Pro	500	505	510

EP 1 217 066 A1

5	Ile Ala Thr Glu Val Trp Leu Ile Asn Lys Ser Met Glu Leu Leu Asp	515	520	525
	Glu Arg Lys Phe Trp Ala Gly Ile Val Phe Thr Gly Ile Thr Pro Gly	530	535	540
10	Ser Ile Glu Leu Pro His His Val Lys Tyr Lys Ile Arg Met Asp Ile	545	550	555
	Asp Asn Val Glu Arg Thr Asn Lys Ile Lys Asp Gly Tyr Trp Asp Pro	565	570	575
15	Gly Pro Arg Ala Asp Pro Phe Glu Asp Met Arg Tyr Val Trp Gly Gly	580	585	590
20	Phe Ala Tyr Leu Gln Asp Val Val Glu Gln Ala Ile Ile Arg Val Leu	595	600	605
25	Thr Gly Thr Glu Lys Lys Thr Gly Val Tyr Met Gln Gln Met Pro Tyr	610	615	620
	Pro Cys Tyr Val Asp Asp Ile Phe Leu Arg Val Met Ser Arg Ser Met	625	630	635
30	Pro Leu Phe Met Thr Leu Ala Trp Ile Tyr Ser Val Ala Val Ile Ile	645	650	655
35	Lys Gly Ile Val Tyr Glu Lys Glu Ala Arg Leu Lys Glu Thr Met Arg	660	665	670
	Ile Met Gly Leu Asp Asn Ser Ile Leu Trp Phe Ser Trp Phe Ile Ser	675	680	685
40	Ser Leu Ile Pro Leu Leu Val Ser Ala Gly Leu Leu Val Val Ile Leu	690	695	700
45	Lys Leu Gly Asn Leu Leu Pro Tyr Ser Asp Pro Ser Val Val Phe Val	705	710	715
	Phe Leu Ser Val Phe Ala Val Val Thr Ile Leu Gln Cys Phe Leu Ile	725	730	735
50	Ser Thr Leu Phe Ser Arg Ala Asn Leu Ala Ala Ala Cys Gly Gly Ile	740	745	750
55	Ile Tyr Phe Thr Leu Tyr Leu Pro Tyr Val Leu Cys Val Ala Trp Gln	755	760	765

EP 1 217 066 A1

5	Asp Tyr Val Gly Phe Thr Leu Lys Ile Phe Ala Ser Leu Leu Ser Pro	770	775	780
	Val Ala Phe Gly Phe Gly Cys Glu Tyr Phe Ala Leu Phe Glu Glu Gln	785	790	795 800
10	Gly Ile Gly Val Gln Trp Asp Asn Leu Phe Glu Ser Pro Val Glu Glu	805	810	815
15	Asp Gly Phe Asn Leu Thr Thr Ser Val Ser Met Met Leu Phe Asp Thr	820	825	830
	Phe Leu Tyr Gly Val Met Thr Trp Tyr Ile Glu Ala Val Phe Pro Gly	835	840	845
20	Gln Tyr Gly Ile Pro Arg Pro Trp Tyr Phe Pro Cys Thr Lys Ser Tyr	850	855	860
25	Trp Phe Gly Glu Glu Ser Asp Glu Lys Ser His Pro Gly Ser Asn Gln	865	870	875 880
	Lys Arg Ile Ser Glu Ile Cys Met Glu Glu Glu Pro Thr His Leu Lys	885	890	895
30	Leu Gly Val Ser Ile Gln Asn Leu Val Lys Val Tyr Arg Asp Gly Met	900	905	910
35	Lys Val Ala Val Asp Gly Leu Ala Leu Asn Phe Tyr Glu Gly Gln Ile	915	920	925
	Thr Ser Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Met Ser	930	935	940
40	Ile Leu Thr Gly Leu Phe Pro Pro Thr Ser Gly Thr Ala Tyr Ile Leu	945	950	955 960
45	Gly Lys Asp Ile Arg Ser Glu Met Ser Thr Ile Arg Gln Asn Leu Gly	965	970	975
	Val Cys Pro Gln His Asn Val Leu Phe Asp Met Leu Thr Val Glu Glu	980	985	990
50	His Ile Trp Phe Tyr Ala Arg Leu Lys Gly Leu Ser Glu Lys His Val	995	1000	1005
55	Lys Ala Glu Met Glu Gln Met Ala Leu Asp Val Gly Leu Pro Ser Ser	1010	1015	1020

EP 1 217 066 A1

5	Lys Leu Lys Ser Lys Thr Ser Gln Leu Ser Gly Gly Met Gln Arg Lys	1025	1030	1035	1040
	Leu Ser Val Ala Leu Ala Phe Val Gly Gly Ser Lys Val Val Ile Leu	1045	1050	1055	
10	Asp Glu Pro Thr Ala Gly Val Asp Pro Tyr Ser Arg Arg Gly Ile Trp	1060	1065	1070	
15	Glu Leu Leu Leu Lys Tyr Arg Gln Gly Arg Thr Ile Ile Leu Ser Thr	1075	1080	1085	
	His His Met Asp Glu Ala Asp Val Leu Gly Asp Arg Ile Ala Ile Ile	1090	1095	1100	
20	Ser His Gly Lys Leu Cys Cys Val Gly Ser Ser Leu Phe Leu Lys Asn	1105	1110	1115	1120
25	Gln Leu Gly Thr Gly Tyr Tyr Leu Thr Leu Val Lys Lys Asp Val Glu	1125	1130	1135	
	Ser Ser Leu Ser Ser Cys Arg Asn Ser Ser Ser Thr Val Ser Tyr Leu	1140	1145	1150	
30	Lys Lys Glu Asp Ser Val Ser Gln Ser Ser Ser Asp Ala Gly Leu Gly	1155	1160	1165	
35	Ser Asp His Glu Ser Asp Thr Leu Thr Ile Asp Val Ser Ala Ile Ser	1170	1175	1180	
40	Asn Leu Ile Arg Lys His Val Ser Glu Ala Arg Leu Val Glu Asp Ile	1185	1190	1195	1200
	Gly His Glu Leu Thr Tyr Val Leu Pro Tyr Glu Ala Ala Lys Glu Gly	1205	1210	1215	
45	Ala Phe Val Glu Leu Phe His Glu Ile Asp Asp Arg Leu Ser Asp Leu	1220	1225	1230	
50	Gly Ile Ser Ser Tyr Gly Ile Ser Glu Thr Thr Leu Glu Glu Ile Phe	1235	1240	1245	
	Leu Lys Val Ala Glu Glu Ser Gly Val Asp Ala Glu Thr Ser Asp Gly	1250	1255	1260	
55	Thr Leu Pro Ala Arg Arg Asn Arg Arg Ala Phe Gly Asp Lys Gln Ser	1265	1270	1275	1280

EP 1 217 066 A1

5 Cys Leu Arg Pro Phe Thr Glu Asp Asp Ala Ala Asp Pro Asn Asp Ser
1285 1290 1295

Asp Ile Asp Pro Glu Ser Arg Glu Thr Asp Leu Leu Ser Gly Met Asp
1300 1305 1310

10 Gly Lys Gly Ser Tyr Gln Val Lys Gly Trp Lys Leu Thr Gln Gln Gln
1315 1320 1325

15 Phe Val Ala Leu Leu Trp Lys Arg Leu Leu Ile Ala Arg Arg Ser Arg
1330 1335 1340

Lys Gly Phe Phe Ala Gln Ile Val Leu Pro Ala Val Phe Val Cys Ile
1345 1350 1355 1360

20 Ala Leu Val Phe Ser Leu Ile Val Pro Pro Phe Gly Lys Tyr Pro Ser
1365 1370 1375

25 Leu Glu Leu Gln Pro Trp Met Tyr Asn Glu Gln Tyr Thr Phe Val Ser
1380 1385 1390

Asn Asp Ala Pro Glu Asp Thr Gly Thr Leu Glu Leu Leu Asn Ala Leu
1395 1400 1405

30 Thr Lys Asp Pro Gly Phe Gly Thr Arg Cys Met Glu Gly Asn Pro Ile
1410 1415 1420

35 Pro Asp Thr Pro Cys Gln Ala Gly Glu Glu Glu Trp Thr Thr Ala Pro
1425 1430 1435 1440

Val Pro Gln Thr Ile Met Asp Leu Phe Gln Asn Gly Asn Trp Thr Met
1445 1450 1455

40 Gln Asn Pro Ser Pro Ala Cys Gln Cys Ser Ser Asp Lys Ile Lys Lys
1460 1465 1470

45 Met Leu Pro Val Cys Pro Pro Gly Ala Gly Gly Leu Pro Pro Pro Gln
1475 1480 1485

Arg Lys Gln Asn Thr Ala Asp Ile Leu Gln Asp Leu Thr Gly Arg Asn
1490 1495 1500

50 Ile Ser Asp Tyr Leu Val Lys Thr Tyr Val Gln Ile Ile Ala Lys Ser
1505 1510 1515 1520

55 Leu Lys Asn Lys Ile Trp Val Asn Glu Phe Arg Tyr Gly Gly Phe Ser
1525 1530 1535

EP 1 217 066 A1

	Leu	Gly	Val	Ser	Asn	Thr	Gln	Ala	Leu	Pro	Pro	Ser	Gln	Glu	Val	Asn	
					1540					1545						1550	
5	Asp	Ala	Thr	Lys	Gln	Met	Lys	Lys	His	Leu	Lys	Leu	Ala	Lys	Asp	Ser	
					1555				1560					1565			
10	Ser	Ala	Asp	Arg	Phe	Leu	Asn	Ser	Leu	Gly	Arg	Phe	Met	Thr	Gly	Leu	
					1570				1575				1580				
15	Asp	Thr	Arg	Asn	Asn	Val	Lys	Val	Trp	Phe	Asn	Asn	Lys	Gly	Trp	His	
					1585			1590				1595				1600	
20	Ala	Ile	Ser	Ser	Phe	Leu	Asn	Val	Ile	Asn	Asn	Ala	Ile	Leu	Arg	Ala	
					1605					1610						1615	
25	Asn	Leu	Gln	Lys	Gly	Glu	Asn	Pro	Ser	His	Tyr	Gly	Ile	Thr	Ala	Phe	
					1620					1625					1630		
30	Asn	His	Pro	Leu	Asn	Leu	Thr	Lys	Gln	Gln	Leu	Ser	Glu	Val	Ala	Pro	
					1635				1640					1645			
35	Met	Thr	Thr	Ser	Val	Asp	Val	Leu	Val	Ser	Ile	Cys	Val	Ile	Phe	Ala	
					1650				1655				1660				
40	Met	Ser	Phe	Val	Pro	Ala	Ser	Phe	Val	Val	Phe	Leu	Ile	Gln	Glu	Arg	
					1665				1670				1675			1680	
45	Val	Ser	Lys	Ala	Lys	His	Leu	Gln	Phe	Ile	Ser	Gly	Val	Lys	Pro	Val	
					1685					1690						1695	
50	Ile	Tyr	Trp	Leu	Ser	Asn	Phe	Val	Trp	Asp	Met	Cys	Asn	Tyr	Val	Val	
					1700					1705					1710		
55	Pro	Ala	Thr	Leu	Val	Ile	Ile	Ile	Phe	Ile	Cys	Phe	Gln	Gln	Lys	Ser	
					1715				1720					1725			
60	Tyr	Val	Ser	Ser	Thr	Asn	Leu	Pro	Val	Leu	Ala	Leu	Leu	Leu	Leu	Leu	
					1730				1735					1740			
65	Tyr	Gly	Trp	Ser	Ile	Thr	Pro	Leu	Met	Tyr	Pro	Ala	Ser	Phe	Val	Phe	
					1745				1750				1755			1760	
70	Lys	Ile	Pro	Ser	Thr	Ala	Tyr	Val	Val	Leu	Thr	Ser	Val	Asn	Leu	Phe	
					1765					1770						1775	
75	Ile	Gly	Ile	Asn	Gly	Ser	Val	Ala	Thr	Phe	Val	Leu	Glu	Leu	Phe	Thr	
					1780					1785						1790	

EP 1 217 066 A1

	Asp Asn Lys Leu Asn Asn Ile Asn Asp Ile Leu Lys Ser Val Phe Leu	
	1795	1800 1805
5	Ile Phe Pro His Phe Cys Leu Gly Arg Gly Leu Ile Asp Met Val Lys	
	1810	1815 1820
10	Asn Gln Ala Met Ala Asp Ala Leu Glu Arg Phe Gly Glu Asn Arg Phe	
	1825	1830 1835 1840
	Val Ser Pro Leu Ser Trp Asp Leu Val Gly Arg Asn Leu Phe Ala Met	
		1845 1850 1855
15	Ala Val Glu Gly Val Val Phe Phe Leu Ile Thr Val Leu Ile Gln Tyr	
		1860 1865 1870
20	Arg Phe Phe Ile Arg Pro Arg Pro Val Asn Ala Lys Leu Ser Pro Leu	
		1875 1880 1885
	Asn Asp Glu Asp Glu Asp Val Arg Arg Glu Arg Gln Arg Ile Leu Asp	
25		1890 1895 1900
	Gly Gly Gly Gln Asn Asp Ile Leu Glu Ile Lys Glu Leu Thr Lys Ile	
	1905	1910 1915 1920
30	Tyr Arg Arg Lys Arg Lys Pro Ala Val Asp Arg Ile Cys Val Gly Ile	
		1925 1930 1935
	Pro Pro Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys	
35		1940 1945 1950
	Ser Ser Thr Phe Lys Met Leu Thr Gly Asp Thr Thr Val Thr Arg Gly	
		1955 1960 1965
40	Asp Ala Phe Leu Asn Arg Asn Ser Ile Leu Ser Asn Ile His Glu Val	
		1970 1975 1980
45	His Gln Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Thr Glu Leu	
	1985	1990 1995 2000
	Leu Thr Gly Arg Glu His Val Glu Phe Phe Ala Leu Leu Arg Gly Val	
		2005 2010 2015
50	Pro Glu Lys Glu Val Gly Lys Val Gly Glu Trp Ala Ile Arg Lys Leu	
		2020 2025 2030
55	Gly Leu Val Lys Tyr Gly Glu Lys Tyr Ala Gly Asn Tyr Ser Gly Gly	
		2035 2040 2045

EP 1 217 066 A1

Asn Lys Arg Lys Leu Ser Thr Ala Met Ala Leu Ile Gly Gly Pro Pro
 2050 2055 2060
 5
 Val Val Phe Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Lys Ala Arg
 2065 2070 2075 2080
 Arg Phe Leu Trp Asn Cys Ala Leu Ser Val Val Lys Glu Gly Arg Ser
 10 2085 2090 2095
 Val Val Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr
 2100 2105 2110
 15
 Arg Met Ala Ile Met Val Asn Gly Arg Phe Arg Cys Leu Gly Ser Val
 2115 2120 2125
 Gln His Leu Lys Asn Arg Phe Gly Asp Gly Tyr Thr Ile Val Val Arg
 20 2130 2135 2140
 Ile Ala Gly Ser Asn Pro Asp Leu Lys Pro Val Gln Asp Phe Phe Gly
 25 2145 2150 2155 2160
 Leu Ala Phe Pro Gly Ser Val Pro Lys Glu Lys His Arg Asn Met Leu
 2165 2170 2175
 30
 Gln Tyr Gln Leu Pro Ser Ser Leu Ser Ser Leu Ala Arg Ile Phe Ser
 2180 2185 2190
 Ile Leu Ser Gln Ser Lys Lys Arg Leu His Ile Glu Asp Tyr Ser Val
 35 2195 2200 2205
 Ser Gln Thr Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys Asp Gln
 2210 2215 2220
 40
 Ser Asp Asp Asp His Leu Lys Asp Leu Ser Leu His Lys Asn Gln Thr
 2225 2230 2235 2240
 Val Val Asp Val Ala Val Leu Thr Ser Phe Leu Gln Asp Glu Lys Val
 45 2245 2250 2255
 Lys Glu Ser Tyr Val
 2260
 50
 <210> 45
 55 <211> 2436
 <212> PRT

EP 1 217 066 A1

<213> Homo sapiens

<400> 45

5 Met Gly Phe Leu His Gln Leu Gln Leu Leu Leu Trp Lys Asn Val Thr
1 5 10 15

10 Leu Lys Arg Arg Ser Pro Trp Val Leu Ala Phe Glu Ile Phe Ile Pro
20 25 30

15 Leu Val Leu Phe Phe Ile Leu Leu Gly Leu Arg Gln Lys Lys Pro Thr
35 40 45

Ile Ser Val Lys Glu Val Pro Phe Tyr Thr Ala Ala Pro Leu Thr Ser
50 55 60

20 Ala Gly Ile Leu Pro Val Met Gln Ser Leu Cys Pro Asp Gly Gln Arg
65 70 75 80

25 Asp Glu Phe Gly Phe Leu Gln Tyr Ala Asn Ser Thr Val Thr Gln Leu
85 90 95

Leu Glu Arg Leu Asp Arg Val Val Glu Glu Gly Asn Leu Phe Asp Pro
100 105 110

30 Ala Arg Pro Ser Leu Gly Ser Glu Leu Glu Ala Leu Arg Gln His Leu
115 120 125

35 Glu Ala Leu Ser Ala Gly Pro Gly Thr Ser Gly Ser His Leu Asp Arg
130 135 140

Ser Thr Val Ser Ser Phe Ser Leu Asp Ser Val Ala Arg Asn Pro Gln
145 150 155 160

40 Glu Leu Trp Arg Phe Leu Thr Gln Asn Leu Ser Leu Pro Asn Ser Thr
165 170 175

45 Ala Gln Ala Leu Leu Ala Ala Arg Val Asp Pro Pro Glu Val Tyr His
180 185 190

Leu Leu Phe Gly Pro Ser Ser Ala Leu Asp Ser Gln Ser Gly Leu His
195 200 205

50 Lys Gly Gln Glu Pro Trp Ser Arg Leu Gly Gly Asn Pro Leu Phe Arg
210 215 220

55 Met Glu Glu Leu Leu Leu Ala Pro Ala Leu Leu Glu Gln Leu Thr Cys
225 230 235 240

EP 1 217 066 A1

	Thr	Pro	Gly	Ser	Gly	Glu	Leu	Gly	Arg	Ile	Leu	Thr	Val	Pro	Glu	Ser	
					245					250					255		
5	Gln	Lys	Gly	Ala	Leu	Gln	Gly	Tyr	Arg	Asp	Ala	Val	Cys	Ser	Gly	Gln	
				260					265					270			
10	Ala	Ala	Ala	Arg	Ala	Arg	Arg	Phe	Ser	Gly	Leu	Ser	Ala	Glu	Leu	Arg	
				275				280					285				
	Asn	Gln	Leu	Asp	Val	Ala	Lys	Val	Ser	Gln	Gln	Leu	Gly	Leu	Asp	Ala	
		290					295					300					
15	Pro	Asn	Gly	Ser	Asp	Ser	Ser	Pro	Gln	Ala	Pro	Pro	Pro	Arg	Arg	Leu	
	305					310					315				320		
20	Gln	Ala	Leu	Leu	Gly	Asp	Leu	Leu	Asp	Ala	Gln	Lys	Val	Leu	Gln	Asp	
					325					330					335		
	Val	Asp	Val	Leu	Ser	Ala	Leu	Ala	Leu	Leu	Leu	Pro	Gln	Gly	Ala	Cys	
				340				345						350			
25	Thr	Gly	Arg	Thr	Pro	Gly	Pro	Pro	Ala	Ser	Gly	Ala	Gly	Gly	Ala	Ala	
			355				360						365				
30	Asn	Gly	Thr	Gly	Ala	Gly	Ala	Val	Met	Gly	Pro	Asn	Ala	Thr	Ala	Glu	
		370					375					380					
	Glu	Gly	Ala	Pro	Ser	Ala	Ala	Ala	Leu	Ala	Thr	Pro	Asp	Thr	Leu	Gln	
35		385				390					395				400		
	Gly	Gln	Cys	Ser	Ala	Phe	Val	Gln	Leu	Trp	Ala	Gly	Leu	Gln	Pro	Ile	
					405					410					415		
40	Leu	Cys	Gly	Asn	Asn	Arg	Thr	Ile	Glu	Pro	Glu	Ala	Leu	Arg	Arg	Gly	
				420					425					430			
	Asn	Met	Ser	Ser	Leu	Gly	Phe	Thr	Ser	Lys	Glu	Gln	Arg	Asn	Leu	Gly	
45			435					440					445				
	Leu	Leu	Val	His	Leu	Met	Thr	Ser	Asn	Pro	Lys	Ile	Leu	Tyr	Ala	Pro	
			450				455					460					
50	Ala	Gly	Ser	Glu	Val	Asp	Arg	Val	Ile	Leu	Lys	Ala	Asn	Glu	Thr	Phe	
		465				470					475				480		
	Ala	Phe	Val	Gly	Asn	Val	Thr	His	Tyr	Ala	Gln	Val	Trp	Leu	Asn	Ile	
55					485					490					495		

EP 1 217 066 A1

	Ser	Ala	Glu	Ile	Arg	Ser	Phe	Leu	Glu	Gln	Gly	Arg	Leu	Gln	Gln	His	
				500					505					510			
5	Leu	Arg	Trp	Leu	Gln	Gln	Tyr	Val	Ala	Glu	Leu	Arg	Leu	His	Pro	Glu	
			515				520						525				
10	Ala	Leu	Asn	Leu	Ser	Leu	Asp	Glu	Leu	Pro	Pro	Ala	Leu	Arg	Gln	Asp	
		530					535					540					
	Asn	Phe	Ser	Leu	Pro	Ser	Gly	Met	Ala	Leu	Leu	Gln	Gln	Leu	Asp	Thr	
	545					550					555				560		
15	Ile	Asp	Asn	Ala	Ala	Cys	Gly	Trp	Ile	Gln	Phe	Met	Ser	Lys	Val	Ser	
				565					570						575		
20	Val	Asp	Ile	Phe	Lys	Gly	Phe	Pro	Asp	Glu	Glu	Ser	Ile	Val	Asn	Tyr	
			580						585					590			
	Thr	Leu	Asn	Gln	Ala	Tyr	Gln	Asp	Asn	Val	Thr	Val	Phe	Ala	Ser	Val	
		595						600					605				
25	Ile	Phe	Gln	Thr	Arg	Lys	Asp	Gly	Ser	Leu	Pro	Pro	His	Val	His	Tyr	
	610						615					620					
30	Lys	Ile	Arg	Gln	Asn	Ser	Ser	Phe	Thr	Glu	Lys	Thr	Asn	Glu	Ile	Arg	
	625					630					635				640		
	Arg	Ala	Tyr	Trp	Arg	Pro	Gly	Pro	Asn	Thr	Gly	Gly	Arg	Phe	Tyr	Phe	
35				645						650				655			
	Leu	Tyr	Gly	Phe	Val	Trp	Ile	Gln	Asp	Met	Met	Glu	Arg	Ala	Ile	Ile	
			660						665				670				
40	Asp	Thr	Phe	Val	Gly	His	Asp	Val	Val	Glu	Pro	Gly	Ser	Tyr	Val	Gln	
		675						680					685				
	Met	Phe	Pro	Tyr	Pro	Cys	Tyr	Thr	Arg	Asp	Asp	Phe	Leu	Phe	Val	Ile	
45		690					695					700					
	Glu	His	Met	Met	Pro	Leu	Cys	Met	Val	Ile	Ser	Trp	Val	Tyr	Ser	Val	
	705					710					715				720		
50	Ala	Met	Thr	Ile	Gln	His	Ile	Val	Ala	Glu	Lys	Glu	His	Arg	Leu	Lys	
				725					730					735			
	Glu	Val	Met	Lys	Thr	Met	Gly	Leu	Asn	Asn	Ala	Val	His	Trp	Val	Ala	
55				740					745					750			

EP 1 217 066 A1

	Trp	Phe	Ile	Thr	Gly	Phe	Val	Gln	Leu	Ser	Ile	Ser	Val	Thr	Ala	Leu	
5	Thr	Ala	Ile	Leu	Lys	Tyr	Gly	Gln	Val	Leu	Met	His	Ser	His	Val	Val	
10	Ile	Ile	Trp	Leu	Phe	Leu	Ala	Val	Tyr	Ala	Val	Ala	Thr	Ile	Met	Phe	
	Cys	Phe	Leu	Val	Ser	Val	Leu	Tyr	Ser	Lys	Ala	Lys	Leu	Ala	Ser	Ala	
15	Cys	Gly	Gly	Ile	Ile	Tyr	Phe	Leu	Ser	Tyr	Val	Pro	Tyr	Met	Tyr	Val	
20	Ala	Ile	Arg	Glu	Glu	Val	Ala	His	Asp	Lys	Ile	Thr	Ala	Phe	Glu	Lys	
	Cys	Ile	Ala	Ser	Leu	Met	Ser	Thr	Thr	Ala	Phe	Gly	Leu	Gly	Ser	Lys	
25	Tyr	Phe	Ala	Leu	Tyr	Glu	Val	Ala	Gly	Val	Gly	Ile	Gln	Trp	His	Thr	
30	Phe	Ser	Gln	Ser	Pro	Val	Glu	Gly	Asp	Asp	Phe	Asn	Leu	Leu	Leu	Ala	
	Val	Thr	Met	Leu	Met	Val	Asp	Ala	Val	Val	Tyr	Gly	Ile	Leu	Thr	Trp	
35	Tyr	Ile	Glu	Ala	Val	His	Pro	Gly	Met	Tyr	Gly	Leu	Pro	Arg	Pro	Trp	
40	Tyr	Phe	Pro	Leu	Gln	Lys	Ser	Tyr	Trp	Leu	Gly	Ser	Gly	Arg	Thr	Glu	
	Ala	Trp	Glu	Trp	Ser	Trp	Pro	Trp	Ala	Arg	Thr	Pro	Arg	Leu	Ser	Val	
45	Met	Glu	Glu	Asp	Gln	Ala	Cys	Ala	Met	Glu	Ser	Arg	Arg	Phe	Glu	Glu	
50	Thr	Arg	Gly	Met	Glu	Glu	Glu	Pro	Thr	His	Leu	Pro	Leu	Val	Val	Cys	
55	Val	Asp	Lys	Leu	Thr	Lys	Val	Tyr	Lys	Asp	Asp	Lys	Lys	Leu	Ala	Leu	

EP 1 217 066 A1

	Asn Lys Leu Ser Leu Asn Leu Tyr Glu Asn Gln Val Val Ser Phe Leu
	1010 1015 1020
5	Gly His Asn Gly Ala Gly Lys Thr Thr Thr Met Ser Ile Leu Thr Gly
	1025 1030 1035 1040
10	Leu Phe Pro Pro Thr Ser Gly Ser Ala Thr Ile Tyr Gly His Asp Ile
	1045 1050 1055
	Arg Thr Glu Met Asp Glu Ile Arg Lys Asn Leu Gly Met Cys Pro Gln
	1060 1065 1070
15	His Asn Val Leu Phe Asp Arg Leu Thr Val Glu Glu His Leu Trp Phe
	1075 1080 1085
20	Tyr Ser Arg Leu Lys Ser Met Ala Gln Glu Glu Ile Arg Arg Glu Met
	1090 1095 1100
	Asp Lys Met Ile Glu Asp Leu Glu Leu Ser Asn Lys Arg His Ser Leu
	1105 1110 1115 1120
25	Val Gln Thr Leu Ser Gly Gly Met Lys Arg Lys Leu Ser Val Ala Ile
	1125 1130 1135
30	Ala Phe Val Gly Gly Ser Arg Ala Ile Ile Leu Asp Glu Pro Thr Ala
	1140 1145 1150
	Gly Val Asp Pro Tyr Ala Arg Arg Ala Ile Trp Asp Leu Ile Leu Lys
	1155 1160 1165
35	Tyr Lys Pro Gly Arg Thr Ile Leu Leu Ser Thr His His Met Asp Glu
	1170 1175 1180
40	Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Ile Ser His Gly Lys Leu
	1185 1190 1195 1200
	Lys Cys Cys Gly Ser Pro Leu Phe Leu Lys Gly Thr Tyr Gly Asp Gly
	1205 1210 1215
45	Tyr Arg Leu Thr Leu Val Lys Arg Pro Ala Glu Pro Gly Gly Pro Gln
	1220 1225 1230
50	Glu Pro Gly Leu Ala Ser Ser Pro Pro Gly Arg Ala Pro Leu Ser Ser
	1235 1240 1245
55	Cys Ser Glu Leu Gln Val Ser Gln Phe Ile Arg Lys His Val Ala Ser
	1250 1255 1260

EP 1 217 066 A1

	Cys	Leu	Leu	Val	Ser	Asp	Thr	Ser	Thr	Glu	Leu	Ser	Tyr	Ile	Leu	Pro	
	1265						1270					1275				1280	
5	Ser	Glu	Ala	Ala	Lys	Lys	Gly	Ala	Phe	Glu	Arg	Leu	Phe	Gln	His	Leu	
					1285					1290				1295			
10	Glu	Arg	Ser	Leu	Asp	Ala	Leu	His	Leu	Ser	Ser	Phe	Gly	Leu	Met	Asp	
				1300					1305				1310				
15	Thr	Thr	Leu	Glu	Glu	Val	Phe	Leu	Lys	Val	Ser	Glu	Glu	Asp	Gln	Ser	
		1315					1320					1325					
20	Leu	Glu	Asn	Ser	Glu	Ala	Asp	Val	Lys	Glu	Ser	Arg	Lys	Asp	Val	Leu	
	1330					1335					1340						
25	Pro	Gly	Ala	Glu	Gly	Pro	Ala	Ser	Gly	Glu	Gly	His	Ala	Gly	Asn	Leu	
	1345				1350				1355					1360			
30	Ala	Arg	Cys	Ser	Glu	Leu	Thr	Gln	Ser	Gln	Ala	Ser	Leu	Gln	Ser	Ala	
				1365				1370				1375					
35	Ser	Ser	Val	Gly	Ser	Ala	Arg	Gly	Asp	Glu	Gly	Ala	Gly	Tyr	Thr	Asp	
		1380				1385				1390							
40	Val	Tyr	Gly	Asp	Tyr	Arg	Pro	Leu	Phe	Asp	Asn	Pro	Gln	Asp	Pro	Asp	
	1395					1400				1405							
45	Asn	Val	Ser	Leu	Gln	Glu	Val	Glu	Ala	Glu	Ala	Leu	Ser	Arg	Val	Gly	
	1410				1415				1420								
50	Gln	Gly	Ser	Arg	Lys	Leu	Asp	Gly	Gly	Trp	Leu	Lys	Val	Arg	Gln	Phe	
	1425				1430				1435				1440				
55	His	Gly	Leu	Leu	Val	Lys	Arg	Phe	His	Cys	Ala	Arg	Arg	Asn	Ser	Lys	
				1445				1450				1455					
60	Ala	Leu	Phe	Ser	Gln	Ile	Leu	Leu	Pro	Ala	Phe	Phe	Val	Cys	Val	Ala	
		1460				1465				1470							
65	Met	Thr	Val	Ala	Leu	Ser	Val	Pro	Glu	Ile	Gly	Asp	Leu	Pro	Pro	Leu	
		1475				1480				1485							
70	Val	Leu	Ser	Pro	Ser	Gln	Tyr	His	Asn	Tyr	Thr	Gln	Pro	Arg	Gly	Asn	
	1490					1495				1500							
75	Phe	Ile	Pro	Tyr	Ala	Asn	Glu	Glu	Arg	Arg	Glu	Tyr	Arg	Leu	Arg	Leu	
	1505				1510				1515				1520				

EP 1 217 066 A1

	Ser Pro Asp Ala Ser Pro Gln Gln Leu Val Ser Thr Phe Arg Leu Pro	
	1525	1530 1535
5	Ser Gly Val Gly Ala Thr Cys Val Leu Lys Ser Pro Ala Asn Gly Ser	
	1540	1545 1550
	Leu Gly Pro Thr Leu Asn Leu Ser Ser Gly Glu Ser Arg Leu Leu Ala	
10	1555	1560 1565
	Ala Arg Phe Phe Asp Ser Met Cys Leu Glu Ser Phe Thr Gln Gly Leu	
	1570	1575 1580
15	Pro Leu Ser Asn Phe Val Pro Pro Pro Pro Ser Pro Ala Pro Ser Asp	
	1585	1590 1595 1600
	Ser Pro Ala Ser Pro Asp Glu Asp Leu Gln Ala Trp Asn Val Ser Leu	
20	1605	1610 1615
	Pro Pro Thr Ala Gly Pro Glu Met Trp Thr Ser Ala Pro Ser Leu Pro	
	1620	1625 1630
25	Arg Leu Val Arg Glu Pro Val Arg Cys Thr Cys Ser Ala Gln Gly Thr	
	1635	1640 1645
	Gly Phe Ser Cys Pro Ser Ser Val Gly Gly His Pro Pro Gln Met Arg	
30	1650	1655 1660
	Val Val Thr Gly Asp Ile Leu Thr Asp Ile Thr Gly His Asn Val Ser	
35	1665	1670 1675 1680
	Glu Tyr Leu Leu Phe Thr Ser Asp Arg Phe Arg Leu His Arg Tyr Gly	
	1685	1690 1695
40	Ala Ile Thr Phe Gly Asn Val Leu Lys Ser Ile Pro Ala Ser Phe Gly	
	1700	1705 1710
	Thr Arg Ala Pro Pro Met Val Arg Lys Ile Ala Val Arg Arg Ala Ala	
45	1715	1720 1725
	Gln Val Phe Tyr Asn Asn Lys Gly Tyr His Ser Met Pro Thr Tyr Leu	
	1730	1735 1740
50	Asn Ser Leu Asn Asn Ala Ile Leu Arg Ala Asn Leu Pro Lys Ser Lys	
	1745	1750 1755 1760
	Gly Asn Pro Ala Ala Tyr Gly Ile Thr Val Thr Asn His Pro Met Asn	
55	1765	1770 1775

EP 1 217 066 A1

	Lys Thr Ser Ala Ser Leu Ser Leu Asp Tyr Leu Leu Gln Gly Thr Asp	
	1780	1785 1790
5	Val Val Ile Ala Ile Phe Ile Ile Val Ala Met Ser Phe Val Pro Ala	
	1795	1800 1805
	Ser Phe Val Val Phe Leu Val Ala Glu Lys Ser Thr Lys Ala Lys His	
10	1810	1815 1820
	Leu Gln Phe Val Ser Gly Cys Asn Pro Ile Ile Tyr Trp Leu Ala Asn	
	1825	1830 1835 1840
15	Tyr Val Trp Asp Met Leu Asn Tyr Leu Val Pro Ala Thr Cys Cys Val	
	1845	1850 1855
	Ile Ile Leu Phe Val Phe Asp Leu Pro Ala Tyr Thr Ser Pro Thr Asn	
20	1860	1865 1870
	Phe Pro Ala Val Leu Ser Leu Phe Leu Leu Tyr Gly Trp Ser Ile Thr	
	1875	1880 1885
25	Pro Ile Met Tyr Pro Ala Ser Phe Trp Phe Glu Val Pro Ser Ser Ala	
	1890	1895 1900
30	Tyr Val Phe Leu Ile Val Ile Asn Leu Phe Ile Gly Ile Thr Ala Thr	
	1905	1910 1915 1920
	Val Ala Thr Phe Leu Leu Gln Leu Phe Glu His Asp Lys Asp Leu Lys	
35	1925	1930 1935
	Val Val Asn Ser Tyr Leu Lys Ser Cys Phe Leu Ile Phe Pro Asn Tyr	
	1940	1945 1950
40	Asn Leu Gly His Gly Leu Met Glu Met Ala Tyr Asn Glu Tyr Ile Asn	
	1955	1960 1965
	Glu Tyr Tyr Ala Lys Ile Gly Gln Phe Asp Lys Met Lys Ser Pro Phe	
45	1970	1975 1980
	Glu Trp Asp Ile Val Thr Arg Gly Leu Val Ala Met Ala Val Glu Gly	
	1985	1990 1995 2000
50	Val Val Gly Phe Leu Leu Thr Ile Met Cys Gln Tyr Asn Phe Leu Arg	
	2005	2010 2015
	Arg Pro Gln Arg Met Pro Val Ser Thr Lys Pro Val Glu Asp Asp Val	
55	2020	2025 2030

EP 1 217 066 A1

	Asp Val Ala Ser Glu Arg Gln Arg Val Leu Arg Gly Asp Ala Asp Asn	
	2035	2040 2045
5	Asp Met Val Lys Ile Glu Asn Leu Thr Lys Val Tyr Lys Ser Arg Lys	
	2050	2055 2060
10	Ile Gly Arg Ile Leu Ala Val Asp Arg Leu Cys Leu Gly Val Arg Pro	
	2065	2070 2075 2080
	Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Ser	
		2085 2090 2095
15	Thr Phe Lys Met Leu Thr Gly Asp Glu Ser Thr Thr Gly Gly Glu Ala	
		2100 2105 2110
20	Phe Val Asn Gly His Ser Val Leu Lys Glu Leu Leu Gln Val Gln Gln	
		2115 2120 2125
	Ser Leu Gly Tyr Cys Pro Gln Cys Asp Ala Leu Phe Asp Glu Leu Thr	
25		2130 2135 2140
	Ala Arg Glu His Leu Gln Leu Tyr Thr Arg Leu Arg Gly Ile Ser Trp	
		2145 2150 2155 2160
30	Lys Asp Glu Ala Arg Val Val Lys Trp Ala Leu Glu Lys Leu Glu Leu	
		2165 2170 2175
	Thr Lys Tyr Ala Asp Lys Pro Ala Gly Thr Tyr Ser Gly Gly Asn Lys	
35		2180 2185 2190
	Arg Lys Leu Ser Thr Ala Ile Ala Leu Ile Gly Tyr Pro Ala Phe Ile	
		2195 2200 2205
40	Phe Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Lys Ala Arg Arg Phe	
		2210 2215 2220
	Leu Trp Asn Leu Ile Leu Asp Leu Ile Lys Thr Gly Arg Ser Val Val	
45		2225 2230 2235 2240
	Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu	
		2245 2250 2255
50	Ala Ile Met Val Asn Gly Arg Leu Arg Cys Leu Gly Ser Ile Gln His	
		2260 2265 2270
	Leu Lys Asn Arg Phe Gly Asp Gly Tyr Met Ile Thr Val Arg Thr Lys	
55		2275 2280 2285

EP 1 217 066 A1

Ser Ser Gln Ser Val Lys Asp Val Val Arg Phe Phe Asn Arg Asn Phe
2290 2295 2300

5 Pro Glu Ala Met Leu Lys Glu Arg His His Thr Lys Val Gln Tyr Gln
2305 2310 2315 2320

10 Leu Lys Ser Glu His Ile Ser Leu Ala Gln Val Phe Ser Lys Met Glu
2325 2330 2335

Gln Val Ser Gly Val Leu Gly Ile Glu Asp Tyr Ser Val Ser Gln Thr
2340 2345 2350

15 Thr Leu Asp Asn Val Phe Val Asn Phe Ala Lys Lys Gln Ser Asp Asn
2355 2360 2365

20 Leu Glu Gln Gln Glu Thr Glu Pro Pro Ser Ala Leu Gln Ser Pro Leu
2370 2375 2380

Gly Cys Leu Leu Ser Leu Leu Arg Pro Arg Ser Ala Pro Thr Glu Leu
2385 2390 2395 2400

25 Arg Ala Leu Val Ala Asp Glu Pro Glu Asp Leu Asp Thr Glu Asp Glu
2405 2410 2415

30 Gly Leu Ile Ser Phe Glu Glu Glu Arg Ala Gln Leu Ser Phe Asn Thr
2420 2425 2430

Asp Thr Leu Cys
2435

35

<210> 46
40 <211> 1704
<212> PRT
<213> Homo sapiens

<400> 46
45 Met Ala Val Leu Arg Gln Leu Ala Leu Leu Leu Trp Lys Asn Tyr Thr
1 5 10 15

Leu Gln Lys Arg Lys Val Leu Val Thr Val Leu Glu Leu Phe Leu Pro
50 20 25 30

Leu Leu Phe Pro Gly Ile Leu Ile Trp Leu Arg Leu Lys Ile Gln Ser
35 40 45

55 Glu Asn Val Pro Asn Ala Thr Ile Tyr Pro Gly Gln Ser Ile Gln Glu

EP 1 217 066 A1

	50					55						60							
5	Leu 65	Pro	Leu	Phe	Phe	Thr	Phe	Pro	Pro	Pro	Gly	Asp	Thr	Trp	Glu	Leu			
						70						75				80			
	Ala	Tyr	Ile	Pro	Ser	His	Ser	Asp	Ala	Ala	Lys	Thr	Val	Thr	Glu	Thr			
					85						90					95			
10	Val	Arg	Arg	Ala	Leu	Val	Ile	Asn	Met	Arg	Val	Arg	Gly	Phe	Pro	Ser			
				100					105					110					
	Glu	Lys	Asp	Phe	Glu	Asp	Tyr	Ile	Arg	Tyr	Asp	Asn	Cys	Ser	Ser	Ser			
15			115					120					125						
	Val	Leu	Ala	Ala	Val	Val	Phe	Glu	His	Pro	Phe	Asn	His	Ser	Lys	Glu			
		130					135					140							
20	Pro	Leu	Pro	Leu	Ala	Val	Lys	Tyr	His	Leu	Arg	Phe	Ser	Tyr	Thr	Arg			
	145					150					155					160			
25	Arg	Asn	Tyr	Met	Trp	Thr	Gln	Thr	Gly	Ser	Phe	Phe	Leu	Lys	Glu	Thr			
				165						170					175				
	Glu	Gly	Trp	His	Thr	Thr	Ser	Leu	Phe	Pro	Leu	Phe	Pro	Asn	Pro	Gly			
30				180					185					190					
	Pro	Arg	Glu	Leu	Thr	Ser	Pro	Asp	Gly	Gly	Glu	Pro	Gly	Tyr	Ile	Arg			
			195					200					205						
35	Glu	Gly	Phe	Leu	Ala	Val	Gln	His	Ala	Val	Asp	Arg	Ala	Ile	Met	Glu			
		210					215					220							
	Tyr	His	Ala	Asp	Ala	Ala	Thr	Arg	Gln	Leu	Phe	Gln	Arg	Leu	Thr	Val			
40	225					230					235					240			
	Thr	Ile	Lys	Arg	Phe	Pro	Tyr	Pro	Pro	Phe	Ile	Ala	Asp	Pro	Phe	Leu			
				245						250					255				
45	Val	Ala	Ile	Gln	Tyr	Gln	Leu	Pro	Leu	Leu	Leu	Leu	Ser	Phe	Thr				
				260					265					270					
	Tyr	Thr	Ala	Leu	Thr	Ile	Ala	Arg	Ala	Val	Val	Gln	Glu	Lys	Glu	Arg			
50		275					280						285						
	Arg	Leu	Lys	Glu	Tyr	Met	Arg	Met	Met	Gly	Leu	Ser	Ser	Trp	Leu	His			
		290					295					300							
55	Trp	Ser	Ala	Trp	Phe	Leu	Leu	Phe	Phe	Leu	Phe	Leu	Leu	Ile	Ala	Ala			

EP 1 217 066 A1

	305		310		315		320
5	Ser Phe Met Thr	Leu Leu Phe Cys Val	Lys Val Lys Pro Asn	Val Ala			
		325	330	335			
10	Val Leu Ser Arg	Ser Asp Pro Ser	Leu Val Leu Ala Phe	Leu Leu Cys			
		340	345	350			
15	Phe Ala Ile Ser	Thr Ile Ser Phe	Ser Phe Met Val	Ser Thr Phe Phe			
		355	360	365			
20	Ser Lys Ala Asn	Met Ala Ala Ala	Phe Gly Gly Phe	Leu Tyr Phe Phe			
		370	375	380			
25	Thr Tyr Ile Pro	Tyr Phe Phe Val	Ala Pro Arg Tyr	Asn Trp Met Thr			
		385	390	395	400		
30	Leu Ser Gln Lys	Leu Cys Ser Cys	Leu Leu Ser Asn	Val Ala Met Ala			
		405	410	415			
35	Met Gly Ala Gln	Leu Ile Gly Lys	Phe Glu Ala Lys	Gly Met Gly Ile			
		420	425	430			
40	Gln Trp Arg Asp	Leu Leu Ser Pro	Val Asn Val Asp	Asp Asp Asp Phe Cys			
		435	440	445			
45	Phe Gly Gln Val	Leu Gly Met Leu	Leu Leu Asp Ser	Val Leu Tyr Gly			
		450	455	460			
50	Leu Val Thr Trp	Tyr Met Glu Ala	Val Phe Pro Gly	Gln Phe Gly Val			
		465	470	475	480		
55	Pro Gln Pro Trp	Tyr Phe Phe Ile	Met Pro Ser Tyr	Trp Cys Gly Lys			
		485	490	495			
60	Pro Arg Ala Val	Ala Gly Lys Glu	Glu Glu Asp Ser	Asp Pro Glu Lys			
		500	505	510			
65	Ala Leu Arg Asn	Glu Tyr Phe Glu	Ala Glu Pro Glu	Asp Leu Val Ala			
		515	520	525			
70	Gly Ile Lys Ile	Lys His Leu Ser	Lys Val Phe Arg	Val Gly Asn Lys			
		530	535	540			
75	Asp Arg Ala Ala	Val Arg Asp Leu	Asn Leu Asn Leu	Tyr Glu Gly Gln			
		545	550	555	560		
80	Ile Thr Val Leu	Leu Gly His Asn	Gly Ala Gly Lys	Thr Thr Thr Leu			

EP 1 217 066 A1

	565	570	575
5	Ser Met Leu Thr Gly Leu Phe Pro Pro Thr Ser Gly Arg Ala Tyr Ile 580 585 590		
	Ser Gly Tyr Glu Ile Ser Gln Asp Met Val Gln Ile Arg Lys Ser Leu 595 600 605		
10	Gly Leu Cys Pro Gln His Asp Ile Leu Phe Asp Asn Leu Thr Val Ala 610 615 620		
15	Glu His Leu Tyr Phe Tyr Ala Gln Leu Lys Gly Leu Ser Arg Gln Lys 625 630 635 640		
	Cys Pro Glu Glu Val Lys Gln Met Leu His Ile Ile Gly Leu Glu Asp 645 650 655		
20	Lys Trp Asn Ser Arg Ser Arg Phe Leu Ser Gly Gly Met Arg Arg Lys 660 665 670		
25	Leu Ser Ile Gly Ile Ala Leu Ile Ala Gly Ser Lys Val Leu Ile Leu 675 680 685		
	Asp Glu Pro Thr Ser Gly Met Asp Ala Ile Ser Arg Arg Ala Ile Trp 690 695 700		
30	Asp Leu Leu Gln Arg Gln Lys Ser Asp Arg Thr Ile Val Leu Thr Thr 705 710 715 720		
35	His Phe Met Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Met 725 730 735		
	Ala Lys Gly Glu Leu Gln Cys Cys Gly Ser Ser Leu Phe Leu Lys Gln 740 745 750		
40	Lys Tyr Gly Ala Gly Tyr His Met Thr Leu Val Lys Glu Pro His Cys 755 760 765		
45	Asn Pro Glu Asp Ile Ser Gln Leu Val His His His Val Pro Asn Ala 770 775 780		
	Thr Leu Glu Ser Ser Ala Gly Ala Glu Leu Ser Phe Ile Leu Pro Arg 785 790 795 800		
50	Glu Ser Thr His Arg Phe Glu Gly Leu Phe Ala Lys Leu Glu Lys Lys 805 810 815		
55	Gln Lys Glu Leu Gly Ile Ala Ser Phe Gly Ala Ser Ile Thr Thr Met		

EP 1 217 066 A1

	820	825	830
5	Glu Glu Val Phe Leu Arg Val Gly Lys Leu Val Asp Ser Ser Met Asp 835	840	845
10	Ile Gln Ala Ile Gln Leu Pro Ala Leu Gln Tyr Gln His Glu Arg Arg 850	855	860
15	Ala Ser Asp Trp Ala Val Asp Ser Asn Leu Cys Gly Ala Met Asp Pro 865	870	875 880
20	Ser Asp Gly Ile Gly Ala Leu Ile Glu Glu Glu Arg Thr Ala Val Lys 885	890	895
25	Leu Asn Thr Gly Leu Ala Leu His Cys Gln Gln Phe Trp Ala Met Phe 900	905	910
30	Leu Lys Lys Ala Ala Tyr Ser Trp Arg Glu Trp Lys Met Val Ala Ala 915	920	925
35	Gln Val Leu Val Pro Leu Thr Cys Val Thr Leu Ala Leu Leu Ala Ile 930	935	940
40	Asn Tyr Ser Ser Glu Leu Phe Asp Asp Pro Met Leu Arg Leu Thr Leu 945	950	955 960
45	Gly Glu Tyr Gly Arg Thr Val Val Pro Phe Ser Val Pro Gly Thr Ser 965	970	975
50	Gln Leu Gly Gln Gln Leu Ser Glu His Leu Lys Asp Ala Leu Gln Ala 980	985	990
55	Glu Gly Gln Glu Pro Arg Glu Val Leu Gly Asp Leu Glu Glu Phe Leu 995	1000	1005
60	Ile Phe Arg Ala Ser Val Glu Gly Gly Gly Phe Asn Glu Arg Cys Leu 1010	1015	1020
65	Val Ala Ala Ser Phe Arg Asp Val Gly Glu Arg Thr Val Val Asn Ala 1025	1030	1035 1040
70	Leu Phe Asn Asn Gln Ala Tyr His Ser Pro Ala Thr Ala Leu Ala Val 1045	1050	1055
75	Val Asp Asn Leu Leu Phe Lys Leu Leu Cys Gly Pro His Ala Ser Ile 1060	1065	1070
80	Val Val Ser Asn Phe Pro Gln Pro Arg Ser Ala Leu Gln Ala Ala Lys		

EP 1 217 066 A1

	1075	1080	1085
5	Asp Gln Phe Asn Glu Gly Arg Lys Gly Phe Asp Ile Ala Leu Asn Leu 1090	1095	1100
10	Leu Phe Ala Met Ala Phe Leu Ala Ser Thr Phe Ser Ile Leu Ala Val 1105	1110	1115 1120
	Ser Glu Arg Ala Val Gln Ala Lys His Val Gln Phe Val Ser Gly Val 1125	1130	1135
15	His Val Ala Ser Phe Trp Leu Ser Ala Leu Leu Trp Asp Leu Ile Ser 1140	1145	1150
20	Phe Leu Ile Pro Ser Leu Leu Leu Leu Val Val Phe Lys Ala Phe Asp 1155	1160	1165
	Val Arg Ala Phe Thr Arg Asp Gly His Met Ala Asp Thr Leu Leu Leu 1170	1175	1180
25	Leu Leu Leu Tyr Gly Trp Ala Ile Ile Pro Leu Met Tyr Leu Met Asn 1185	1190	1195 1200
30	Phe Phe Phe Leu Gly Ala Ala Thr Ala Tyr Thr Arg Leu Thr Ile Phe 1205	1210	1215
	Asn Ile Leu Ser Gly Ile Ala Thr Phe Leu Met Val Thr Ile Met Arg 1220	1225	1230
35	Ile Pro Ala Val Lys Leu Glu Glu Leu Ser Lys Thr Leu Asp His Val 1235	1240	1245
40	Phe Leu Val Leu Pro Asn His Cys Leu Gly Met Ala Val Ser Ser Phe 1250	1255	1260
	Tyr Glu Asn Tyr Glu Thr Arg Arg Tyr Cys Thr Ser Ser Glu Val Ala 1265	1270	1275 1280
45	Ala His Tyr Cys Lys Lys Tyr Asn Ile Gln Tyr Gln Glu Asn Phe Tyr 1285	1290	1295
50	Ala Trp Ser Ala Pro Gly Val Gly Arg Phe Val Ala Ser Met Ala Ala 1300	1305	1310
	Ser Gly Cys Ala Tyr Leu Ile Leu Leu Phe Leu Ile Glu Thr Asn Leu 1315	1320	1325
55	Leu Gln Arg Leu Arg Gly Ile Leu Cys Ala Leu Arg Arg Arg Thr		

EP 1 217 066 A1

	1330	1335	1340
5	Leu Thr Glu Leu Tyr Thr Arg Met Pro Val Leu Pro Glu Asp Gln Asp 1345	1350	1355 1360
10	Val Ala Asp Glu Arg Thr Arg Ile Leu Ala Pro Ser Pro Asp Ser Leu 1365	1370	1375
	Leu His Thr Pro Leu Ile Ile Lys Glu Leu Ser Lys Val Tyr Glu Gln 1380	1385	1390
15	Arg Val Pro Leu Leu Ala Val Asp Arg Leu Ser Leu Ala Val Gln Lys 1395	1400	1405
20	Gly Glu Cys Phe Gly Leu Leu Gly Phe Asn Gly Ala Gly Lys Thr Thr 1410	1415	1420
	Thr Phe Lys Met Leu Thr Gly Glu Glu Ser Leu Thr Ser Gly Asp Ala 1425	1430	1435 1440
25	Phe Val Gly Gly His Arg Ile Ser Ser Asp Val Gly Lys Val Arg Gln 1445	1450	1455
30	Arg Ile Gly Tyr Cys Pro Gln Phe Asp Ala Leu Leu Asp His Met Thr 1460	1465	1470
	Gly Arg Glu Met Leu Val Met Tyr Ala Arg Leu Arg Gly Ile Pro Glu 1475	1480	1485
35	Arg His Ile Gly Ala Cys Val Glu Asn Thr Leu Arg Gly Leu Leu Leu 1490	1495	1500
40	Glu Pro His Ala Asn Lys Leu Val Arg Thr Tyr Ser Gly Gly Asn Lys 1505	1510	1515 1520
	Arg Lys Leu Ser Thr Gly Ile Ala Leu Ile Gly Glu Pro Ala Val Ile 1525	1530	1535
45	Phe Leu Asp Glu Pro Ser Thr Gly Met Asp Pro Val Ala Arg Arg Leu 1540	1545	1550
50	Leu Trp Asp Thr Val Ala Arg Ala Arg Glu Ser Gly Lys Ala Ile Ile 1555	1560	1565
	Ile Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu 1570	1575	1580
55	Ala Ile Met Val Gln Gly Gln Phe Lys Cys Leu Gly Ser Pro Gln His		

EP 1 217 066 A1

	1585	1590	1595	1600
5	Leu Lys Ser Lys Phe Gly Ser Gly Tyr Ser Leu Arg Ala Lys Val Gln	1605	1610	1615
10	Ser Glu Gly Gln Gln Glu Ala Leu Glu Glu Phe Lys Ala Phe Val Asp	1620	1625	1630
15	Leu Thr Phe Pro Gly Ser Val Leu Glu Asp Glu His Gln Gly Met Val	1635	1640	1645
20	His Tyr His Leu Pro Gly Arg Asp Leu Ser Trp Ala Lys Val Phe Gly	1650	1655	1660
25	Ile Leu Glu Lys Ala Lys Glu Lys Tyr Gly Val Asp Asp Tyr Ser Val	1665	1670	1675
30	Ser Gln Ile Ser Leu Glu Gln Val Phe Leu Ser Phe Ala His Leu Gln	1685	1690	1695
35	Pro Pro Thr Ala Glu Glu Gly Arg	1700		
40	<210> 47 <211> 2273 <212> PRT <213> Homo sapiens			
45	<400> 47 Met Gly Phe Val Arg Gln Ile Gln Leu Leu Leu Trp Lys Asn Trp Thr	1	5	10
50	Leu Arg Lys Arg Gln Lys Ile Arg Phe Val Val Glu Leu Val Trp Pro	20	25	30
55	Leu Ser Leu Phe Leu Val Leu Ile Trp Leu Arg Asn Ala Asn Pro Leu	35	40	45
60	Tyr Ser His His Glu Cys His Phe Pro Asn Lys Ala Met Pro Ser Ala	50	55	60
65	Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro	65	70	75
70	Cys Phe Gln Ser Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Ser Asn	85	90	95

EP 1 217 066 A1

Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu
 100 105 110
 5
 Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu
 115 120 125
 10
 Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu
 130 135 140
 Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu
 145 150 155 160
 15
 Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser
 165 170 175
 20
 Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala
 180 185 190
 His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala
 195 200 205
 25
 Leu Leu Glu Arg Phe Ile Ile Phe Ser Gln Arg Arg Gly Ala Lys Thr
 210 215 220
 30
 Val Arg Tyr Ala Leu Cys Ser Leu Ser Gln Gly Thr Leu Gln Trp Ile
 225 230 235 240
 Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val
 245 250 255
 35
 Leu Pro Thr Leu Leu Asp Ser Arg Ser Gln Gly Ile Asn Leu Arg Ser
 260 265 270
 40
 Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile
 275 280 285
 His Arg Pro Ser Met Gln Asp Leu Leu Trp Val Thr Arg Pro Leu Met
 290 295 300
 45
 Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser
 305 310 315 320
 50
 Asp Leu Leu Cys Gly Tyr Pro Glu Gly Gly Gly Ser Arg Val Leu Ser
 325 330 335
 55
 Phe Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Phe Leu Gly Ile Asp
 340 345 350

EP 1 217 066 A1

	Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser	
	355	360 365
5	Phe Cys Asn Ala Leu Ile Gln Ser Leu Glu Ser Asn Pro Leu Thr Lys	
	370	375 380
10	Ile Ala Trp Arg Ala Ala Lys Pro Leu Leu Met Gly Lys Ile Leu Tyr	
	385	390 395 400
	Thr Pro Asp Ser Pro Ala Ala Arg Arg Ile Leu Lys Asn Ala Asn Ser	
15		405 410 415
	Thr Phe Glu Glu Leu Glu His Val Arg Lys Leu Val Lys Ala Trp Glu	
	420	425 430
20	Glu Val Gly Pro Gln Ile Trp Tyr Phe Phe Asp Asn Ser Thr Gln Met	
	435	440 445
	Asn Met Ile Arg Asp Thr Leu Gly Asn Pro Thr Val Lys Asp Phe Leu	
25		450 455 460
	Asn Arg Gln Leu Gly Glu Glu Gly Ile Thr Ala Glu Ala Ile Leu Asn	
	465	470 475 480
30	Phe Leu Tyr Lys Gly Pro Arg Glu Ser Gln Ala Asp Asp Met Ala Asn	
		485 490 495
	Phe Asp Trp Arg Asp Ile Phe Asn Ile Thr Asp Arg Thr Leu Arg Leu	
35		500 505 510
	Val Asn Gln Tyr Leu Glu Cys Leu Val Leu Asp Lys Phe Glu Ser Tyr	
	515	520 525
40	Asn Asp Glu Thr Gln Leu Thr Gln Arg Ala Leu Ser Leu Leu Glu Glu	
	530	535 540
	Asn Met Phe Trp Ala Gly Val Val Phe Pro Asp Met Tyr Pro Trp Thr	
45		545 550 555 560
	Ser Ser Leu Pro Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile Asp	
50		565 570 575
	Val Val Glu Lys Thr Asn Lys Ile Lys Asp Arg Tyr Trp Asp Ser Gly	
	580	585 590
55	Pro Arg Ala Asp Pro Val Glu Asp Phe Arg Tyr Ile Trp Gly Gly Phe	
	595	600 605

EP 1 217 066 A1

	Ala Tyr Leu Gln Asp Met Val Glu Gln Gly Ile Thr Arg Ser Gln Val	
	610	620
5	Gln Ala Glu Ala Pro Val Gly Ile Tyr Leu Gln Gln Met Pro Tyr Pro	
	625	640
10	Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro	
	645	655
	Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys	
	660	670
15	Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn	
	675	685
20	Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser	
	690	700
	Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met	
	705	720
25	His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe	
	725	735
30	Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser	
	740	750
	Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile	
	755	765
35	Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp	
	770	780
40	Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val	
	785	800
	Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly	
	805	815
45	Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp	
	820	830
50	Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala	
	835	845
55	Cys Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp	
	850	860

EP 1 217 066 A1

	Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp	
	865	870 875 880
5	Leu Ser Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys	
		885 890 895
10	Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly	
		900 905 910
	Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly	
		915 920 925
15	Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro	
		930 935 940
20	Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala	
		945 950 955 960
	Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu	
25		965 970 975
	Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg	
		980 985 990
30	Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys	
		995 1000 1005
	Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met	
35		1010 1015 1020
	Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu	
		1025 1030 1035 1040
40	Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn	
		1045 1050 1055
	Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val	
45		1060 1065 1070
	Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro	
		1075 1080 1085
50	Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu	
		1090 1095 1100
55	Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Pro Thr His His Met	
		1105 1110 1115 1120

EP 1 217 066 A1

	Asp Glu Ala Asp His Gln Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly	
	1125	1130 1135
5	Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly	
	1140	1145 1150
	Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser	
10	1155	1160 1165
	Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe	
	1170	1175 1180
15	Ser Thr Thr Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln Val	
	1185	1190 1195 1200
	Leu Asp Gly Asp Val Asn Glu Leu Met Asp Val Val Leu His His Val	
20	1205	1210 1215
	Pro Glu Ala Lys Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe Leu	
	1220	1225 1230
25	Leu Pro Asn Lys Asn Phe Lys His Arg Ala Tyr Ala Ser Leu Phe Arg	
	1235	1240 1245
	Glu Leu Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser Ser Phe Gly Ile	
30	1250	1255 1260
	Ser Asp Thr Pro Leu Glu Glu Ile Phe Leu Lys Val Thr Glu Asp Ser	
35	1265	1270 1275 1280
	Asp Ser Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln Lys Arg Glu Asn	
	1285	1290 1295
40	Val Asn Pro Arg His Pro Cys Leu Gly Pro Arg Glu Lys Ala Gly Gln	
	1300	1305 1310
	Thr Pro Gln Asp Ser Asn Val Cys Ser Pro Gly Ala Pro Ala Ala His	
45	1315	1320 1325
	Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro Gly Pro Gln Leu	
	1330	1335 1340
50	Asn Thr Gly Thr Gln Leu Val Leu Gln His Val Gln Ala Leu Leu Val	
	1345	1350 1355 1360
	Lys Arg Phe Gln His Thr Ile Arg Ser His Lys Asp Phe Leu Ala Gln	
55	1365	1370 1375

EP 1 217 066 A1

Ile Val Leu Pro Ala Thr Phe Val Phe Leu Ala Leu Met Leu Ser Ile
1380 1385 1390

5 Val Ile Leu Pro Phe Gly Glu Tyr Pro Ala Leu Thr Leu His Pro Trp
1395 1400 1405

10 Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp Glu Pro Gly Ser
1410 1415 1420

Glu Gln Phe Thr Val Leu Ala Asp Val Leu Leu Asn Lys Pro Gly Phe
1425 1430 1435 1440

15 Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu Pro Glu Tyr Pro Cys Gly
1445 1450 1455

20 Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser Pro Asn Ile Thr Gln
1460 1465 1470

Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn Pro Ser Pro Ser Cys
1475 1480 1485

25 Arg Cys Ser Thr Arg Glu Lys Leu Thr Met Leu Pro Glu Cys Pro Glu
1490 1495 1500

30 Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Thr Gln Arg Ser Thr Glu
1505 1510 1515 1520

Ile Leu Gln Asp Leu Thr Asp Arg Asn Ile Ser Asp Phe Leu Val Lys
1525 1530 1535

35 Thr Tyr Pro Ala Leu Ile Arg Ser Ser Leu Lys Ser Lys Phe Trp Val
1540 1545 1550

40 Asn Glu Gln Arg Tyr Gly Gly Ile Ser Ile Gly Gly Lys Leu Pro Val
1555 1560 1565

Val Pro Ile Thr Gly Glu Ala Leu Val Gly Phe Leu Ser Asp Leu Gly
1570 1575 1580

45 Arg Ile Met Asn Val Ser Gly Gly Pro Ile Thr Arg Glu Ala Ser Lys
1585 1590 1595 1600

50 Glu Ile Pro Asp Phe Leu Lys His Leu Glu Thr Glu Asp Asn Ile Lys
1605 1610 1615

55 Val Trp Phe Asn Asn Lys Gly Trp His Ala Leu Val Ser Phe Leu Asn
1620 1625 1630

EP 1 217 066 A1

	Val	Ala	His	Asn	Ala	Ile	Leu	Arg	Ala	Ser	Leu	Pro	Lys	Asp	Arg	Ser	
5	Pro	Glu	Glu	Tyr	Gly	Ile	Thr	Val	Ile	Ser	Gln	Pro	Leu	Asn	Leu	Thr	
10	Lys	Glu	Gln	Leu	Ser	Glu	Ile	Thr	Val	Leu	Thr	Thr	Ser	Val	Asp	Ala	
15	Val	Val	Ala	Ile	Cys	Val	Ile	Phe	Ser	Met	Ser	Phe	Val	Pro	Ala	Ser	
20	Phe	Val	Leu	Tyr	Leu	Ile	Gln	Glu	Arg	Val	Asn	Lys	Ser	Lys	His	Leu	
25	Gln	Phe	Ile	Ser	Gly	Val	Ser	Pro	Thr	Thr	Tyr	Trp	Val	Thr	Asn	Phe	
30	Leu	Trp	Asp	Ile	Met	Asn	Tyr	Ser	Val	Ser	Ala	Gly	Leu	Val	Val	Gly	
35	Ile	Phe	Ile	Gly	Phe	Gln	Lys	Lys	Ala	Tyr	Thr	Ser	Pro	Glu	Asn	Leu	
40	Pro	Ala	Leu	Val	Ala	Leu	Leu	Leu	Leu	Tyr	Gly	Trp	Ala	Val	Ile	Pro	
45	Met	Met	Tyr	Pro	Ala	Ser	Phe	Leu	Phe	Asp	Val	Pro	Ser	Thr	Ala	Tyr	
50	Val	Ala	Leu	Ser	Cys	Ala	Asn	Leu	Phe	Ile	Gly	Ile	Asn	Ser	Ser	Ala	
55	Ile	Thr	Phe	Ile	Leu	Glu	Leu	Phe	Asp	Asn	Asn	Arg	Thr	Leu	Leu	Arg	
60	Phe	Asn	Ala	Val	Leu	Arg	Lys	Leu	Leu	Ile	Val	Phe	Pro	His	Phe	Cys	
65	Leu	Gly	Arg	Gly	Leu	Ile	Asp	Leu	Ala	Leu	Ser	Gln	Ala	Val	Thr	Asp	
70	Val	Tyr	Ala	Arg	Phe	Gly	Glu	Glu	His	Ser	Ala	Asn	Pro	Phe	His	Trp	
75	Asp	Leu	Ile	Gly	Lys	Asn	Leu	Phe	Ala	Met	Val	Val	Glu	Gly	Val	Val	

EP 1 217 066 A1

	Tyr	Phe	Leu	Leu	Thr	Leu	Leu	Val	Gln	Arg	His	Phe	Phe	Leu	Ser	Gln
	1890							1895							1900	
5	Trp	Ile	Ala	Glu	Pro	Thr	Lys	Glu	Pro	Ile	Val	Asp	Glu	Asp	Asp	Asp
	1905						1910				1915					1920
10	Val	Ala	Glu	Glu	Arg	Gln	Arg	Ile	Ile	Thr	Gly	Gly	Asn	Lys	Thr	Asp
					1925					1930					1935	
15	Ile	Leu	Arg	Leu	His	Glu	Leu	Thr	Lys	Ile	Tyr	Leu	Gly	Thr	Ser	Ser
				1940					1945					1950		
20	Pro	Ala	Val	Asp	Arg	Leu	Cys	Val	Gly	Val	Arg	Pro	Gly	Glu	Cys	Phe
			1955				1960						1965			
25	Gly	Leu	Leu	Gly	Val	Asn	Gly	Ala	Gly	Lys	Thr	Thr	Thr	Phe	Lys	Met
	1970					1975					1980					
30	Leu	Thr	Gly	Asp	Thr	Thr	Val	Thr	Ser	Gly	Asp	Ala	Thr	Val	Ala	Gly
	1985				1990				1995						2000	
35	Lys	Ser	Ile	Leu	Thr	Asn	Ile	Ser	Glu	Val	His	Gln	Asn	Met	Gly	Tyr
				2005					2010					2015		
40	Cys	Pro	Gln	Phe	Asp	Ala	Ile	Asp	Glu	Leu	Leu	Thr	Gly	Arg	Glu	His
			2020					2025					2030			
45	Leu	Tyr	Leu	Tyr	Ala	Arg	Leu	Arg	Gly	Val	Pro	Ala	Glu	Glu	Ile	Glu
	2035					2040					2045					
50	Lys	Val	Ala	Asn	Trp	Ser	Ile	Lys	Ser	Leu	Gly	Leu	Thr	Val	Tyr	Ala
	2050				2055					2060						
55	Asp	Cys	Leu	Ala	Gly	Thr	Tyr	Ser	Gly	Gly	Asn	Lys	Arg	Lys	Leu	Ser
	2065				2070				2075					2080		
60	Thr	Ala	Ile	Ala	Leu	Ile	Gly	Cys	Pro	Pro	Leu	Val	Leu	Leu	Asp	Glu
			2085					2090					2095			
65	Pro	Thr	Thr	Gly	Met	Asp	Pro	Gln	Ala	Arg	Arg	Met	Leu	Trp	Asn	Val
			2100					2105					2110			
70	Ile	Val	Ser	Ile	Ile	Arg	Lys	Gly	Arg	Ala	Val	Val	Leu	Thr	Ser	His
		2115					2120						2125			
75	Ser	Met	Glu	Glu	Cys	Glu	Ala	Leu	Cys	Thr	Arg	Leu	Ala	Ile	Met	Val
	2130					2135					2140					

EP 1 217 066 A1

Lys Gly Ala Phe Arg Cys Met Gly Thr Ile Gln His Leu Lys Ser Lys
 2145 2150 2155 2160
 5 Phe Gly Asp Gly Tyr Ile Val Thr Met Lys Ile Lys Ser Pro Lys Asp
 2165 2170 2175
 Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly Asn
 10 2180 2185 2190
 Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln Phe
 2195 2200 2205
 15 Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu Ser
 2210 2215 2220
 20 His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr Thr
 2225 2230 2235 2240
 Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser His
 25 2245 2250 2255
 Asp Leu Pro Leu His Pro Arg Ala Ala Gly Ala Ser Arg Gln Ala Gln
 30 2260 2265 2270
 Asp
 35
 <210> 48
 <211> 2146
 <212> PRT
 40 <213> Homo sapiens
 <400> 48
 Met Ala Phe Trp Thr Gln Leu Met Leu Leu Leu Trp Lys Asn Phe Met
 1 5 10 15
 45 Tyr Arg Arg Arg Gln Pro Val Gln Leu Leu Val Glu Leu Leu Trp Pro
 20 25 30
 50 Leu Phe Leu Phe Phe Ile Leu Val Ala Val Arg His Ser His Pro Pro
 35 40 45
 Leu Glu His His Glu Cys His Phe Pro Asn Lys Pro Leu Pro Ser Ala
 55 50 55 60

EP 1 217 066 A1

	Gly Thr Val Pro Trp Leu Gln Gly Leu Ile Cys Asn Val Asn Asn Thr	
	65	70 75 80
5	Cys Phe Pro Gln Leu Thr Pro Gly Glu Glu Pro Gly Arg Leu Ser Asn	
		85 90 95
10	Phe Asn Asp Ser Leu Val Ser Arg Leu Leu Ala Asp Ala Arg Thr Val	
		100 105 110
15	Leu Gly Gly Ala Ser Ala His Arg Thr Leu Ala Gly Leu Gly Lys Leu	
		115 120 125
	Ile Ala Thr Leu Arg Ala Ala Arg Ser Thr Ala Gln Pro Gln Pro Thr	
		130 135 140
20	Lys Gln Ser Pro Leu Glu Pro Pro Met Leu Asp Val Ala Glu Leu Leu	
		145 150 155 160
	Thr Ser Leu Leu Arg Thr Glu Ser Leu Gly Leu Ala Leu Gly Gln Ala	
25		165 170 175
	Gln Glu Pro Leu His Ser Leu Leu Glu Ala Ala Glu Asp Leu Ala Gln	
		180 185 190
30	Glu Leu Leu Ala Leu Arg Ser Leu Val Glu Leu Arg Ala Leu Leu Gln	
		195 200 205
	Arg Pro Arg Gly Thr Ser Gly Pro Leu Glu Leu Leu Ser Glu Ala Leu	
35		210 215 220
	Cys Ser Val Arg Gly Pro Ser Ser Thr Val Gly Pro Ser Leu Asn Trp	
		225 230 235 240
40	Tyr Glu Ala Ser Asp Leu Met Glu Leu Val Gly Gln Glu Pro Glu Ser	
		245 250 255
	Ala Leu Pro Asp Ser Ser Leu Ser Pro Ala Cys Ser Glu Leu Ile Gly	
45		260 265 270
	Ala Leu Asp Ser His Pro Leu Ser Arg Leu Leu Trp Arg Arg Leu Lys	
		275 280 285
50	Pro Leu Ile Leu Gly Lys Leu Leu Phe Ala Pro Asp Thr Pro Phe Thr	
		290 295 300
	Arg Lys Leu Met Ala Gln Val Asn Arg Thr Phe Glu Glu Leu Thr Leu	
55		305 310 315 320

EP 1 217 066 A1

5	Leu Arg Asp Val Arg Glu Val Trp Glu Met Leu Gly Pro Arg Ile Phe	325	330	335	
	Thr Phe Met Asn Asp Ser Ser Asn Val Ala Met Leu Gln Arg Leu Leu	340	345	350	
10	Gln Met Gln Asp Glu Gly Arg Arg Gln Pro Arg Pro Gly Gly Arg Asp	355	360	365	
15	His Met Glu Ala Leu Arg Ser Phe Leu Asp Pro Gly Ser Gly Gly Tyr	370	375	380	
	Ser Trp Gln Asp Ala His Ala Asp Val Gly His Leu Val Gly Thr Leu	385	390	395	400
20	Gly Arg Val Thr Glu Cys Leu Ser Leu Asp Lys Leu Glu Ala Ala Pro	405	410	415	
25	Ser Glu Ala Ala Leu Val Ser Arg Ala Leu Gln Leu Leu Ala Glu His	420	425	430	
	Arg Phe Trp Ala Gly Val Val Phe Leu Gly Pro Glu Asp Ser Ser Asp	435	440	445	
30	Pro Thr Glu His Pro Thr Pro Asp Leu Gly Pro Gly His Val Arg Ile	450	455	460	
35	Lys Ile Arg Met Asp Ile Asp Val Val Thr Arg Thr Asn Lys Ile Arg	465	470	475	480
	Asp Arg Phe Trp Asp Pro Gly Pro Ala Ala Asp Pro Leu Thr Asp Leu	485	490	495	
40	Arg Tyr Val Trp Gly Gly Phe Val Tyr Leu Gln Asp Leu Val Glu Arg	500	505	510	
45	Ala Ala Val Arg Val Leu Ser Gly Ala Asn Pro Arg Ala Gly Leu Tyr	515	520	525	
50	Leu Gln Gln Met Pro Tyr Pro Cys Tyr Val Asp Asp Val Phe Leu Arg	530	535	540	
	Val Leu Ser Arg Ser Leu Pro Leu Phe Leu Thr Leu Ala Trp Ile Tyr	545	550	555	560
55	Ser Val Thr Leu Thr Val Lys Ala Val Val Arg Glu Lys Glu Thr Arg	565	570	575	

EP 1 217 066 A1

	Leu Arg Asp Thr Met Arg Ala Met Gly Leu Ser Arg Ala Val Leu Trp	
	580	590
5	Leu Gly Trp Phe Leu Ser Cys Leu Gly Pro Phe Leu Leu Ser Ala Ala	
	595	605
10	Leu Leu Val Leu Val Leu Lys Leu Gly Asp Ile Leu Pro Tyr Ser His	
	610	620
	Pro Gly Val Val Phe Leu Phe Leu Ala Ala Phe Ala Val Ala Thr Val	
15	625	635
	Thr Gln Ser Phe Leu Leu Ser Ala Phe Phe Ser Arg Ala Asn Leu Ala	
	645	655
20	Ala Ala Cys Gly Gly Leu Ala Tyr Phe Ser Leu Tyr Leu Pro Tyr Val	
	660	670
	Leu Cys Val Ala Trp Arg Asp Arg Leu Pro Ala Gly Gly Arg Val Ala	
25	675	685
	Ala Ser Leu Leu Ser Pro Val Ala Phe Gly Phe Gly Cys Glu Ser Leu	
	690	700
30	Ala Leu Leu Glu Glu Gln Gly Glu Gly Ala Gln Trp His Asn Val Gly	
	705	720
	Thr Arg Pro Thr Ala Asp Val Phe Ser Leu Ala Gln Val Ser Gly Leu	
35	725	735
	Leu Leu Leu Asp Ala Ala Leu Tyr Gly Leu Ala Thr Trp Tyr Leu Glu	
	740	750
40	Ala Val Cys Pro Gly Gln Tyr Gly Ile Pro Glu Pro Trp Asn Phe Pro	
	755	765
	Phe Arg Arg Ser Tyr Trp Cys Gly Pro Arg Pro Pro Lys Ser Pro Ala	
45	770	780
	Pro Cys Pro Thr Pro Leu Asp Pro Lys Val Leu Val Glu Glu Ala Pro	
	785	800
50	Pro Gly Leu Ser Pro Gly Val Ser Val Arg Ser Leu Glu Lys Arg Phe	
	805	815
55	Pro Gly Ser Pro Gln Pro Ala Leu Arg Gly Leu Ser Leu Asp Phe Tyr	
	820	830

EP 1 217 066 A1

	Gln Gly His Ile Thr Ala Phe Leu Gly His Asn Gly Ala Gly Lys Thr	
	835	840 845
5		
	Thr Thr Leu Ser Ile Leu Ser Gly Leu Phe Pro Pro Ser Gly Gly Ser	
	850	855 860
10		
	Ala Phe Ile Leu Gly His Asp Val Arg Ser Ser Met Ala Ala Ile Arg	
	865	870 875 880
	Pro His Leu Gly Val Cys Pro Gln Tyr Asn Val Leu Phe Asp Met Leu	
15		885 890 895
	Thr Val Asp Glu His Val Trp Phe Tyr Gly Arg Leu Lys Gly Leu Ser	
	900	905 910
20		
	Ala Ala Val Val Gly Pro Glu Gln Asp Arg Leu Leu Gln Asp Val Gly	
	915	920 925
	Leu Val Ser Lys Gln Ser Val Gln Thr Arg His Leu Ser Gly Gly Met	
25		930 935 940
	Gln Arg Lys Leu Ser Val Ala Ile Ala Phe Val Gly Gly Ser Gln Val	
	945	950 955 960
30		
	Val Ile Leu Asp Glu Pro Thr Ala Gly Val Asp Pro Ala Ser Arg Arg	
	965	970 975
	Gly Ile Trp Glu Leu Leu Leu Lys Tyr Arg Glu Gly Arg Thr Leu Ile	
35		980 985 990
	Leu Ser Thr His His Leu Asp Glu Ala Glu Leu Leu Gly Asp Arg Val	
	995	1000 1005
40		
	Ala Val Val Ala Gly Gly Arg Leu Cys Cys Cys Gly Ser Pro Leu Phe	
	1010	1015 1020
	Leu Arg Arg His Leu Gly Ser Gly Tyr Tyr Leu Thr Leu Val Lys Ala	
45		1025 1030 1035 1040
	Arg Leu Pro Leu Thr Thr Asn Glu Lys Ala Asp Thr Asp Met Glu Gly	
	1045	1050 1055
50		
	Ser Val Asp Thr Arg Gln Glu Lys Lys Asn Gly Ser Gln Gly Ser Arg	
	1060	1065 1070
	Val Gly Thr Pro Gln Leu Leu Ala Leu Val Gln His Trp Val Pro Gly	
55		1075 1080 1085

EP 1 217 066 A1

	Ala Arg Leu Val Glu Glu Leu Pro His Glu Leu Val Leu Val Leu Pro	
	1090	1095 1100
5	Tyr Thr Gly Ala His Asp Gly Ser Phe Ala Thr Leu Phe Arg Glu Leu	
	1105	1110 1115 1120
10	Asp Thr Arg Leu Ala Glu Leu Arg Leu Thr Gly Tyr Gly Ile Ser Asp	
		1125 1130 1135
	Thr Ser Leu Glu Glu Ile Phe Leu Lys Val Val Glu Glu Cys Ala Ala	
15		1140 1145 1150
	Asp Thr Asp Met Glu Asp Gly Ser Cys Gly Gln His Leu Cys Thr Gly	
	1155	1160 1165
20	Ile Ala Gly Leu Asp Val Thr Leu Arg Leu Lys Met Pro Pro Gln Glu	
	1170	1175 1180
	Thr Ala Leu Glu Asn Gly Glu Pro Ala Gly Ser Ala Pro Glu Thr Asp	
25	1185	1190 1195 1200
	Gln Gly Ser Gly Pro Asp Ala Val Gly Arg Val Gln Gly Trp Ala Leu	
		1205 1210 1215
30	Thr Arg Gln Gln Leu Gln Ala Leu Leu Leu Lys Arg Phe Leu Leu Ala	
		1220 1225 1230
	Arg Arg Ser Arg Arg Gly Leu Phe Ala Gln Ile Val Leu Pro Ala Leu	
35		1235 1240 1245
	Phe Val Gly Leu Ala Leu Val Phe Ser Leu Ile Val Pro Pro Phe Gly	
	1250	1255 1260
40	His Tyr Pro Ala Leu Arg Leu Ser Pro Thr Met Tyr Gly Ala Gln Val	
	1265	1270 1275 1280
	Ser Phe Phe Ser Glu Asp Ala Pro Gly Asp Pro Gly Arg Ala Arg Leu	
45		1285 1290 1295
	Leu Glu Ala Leu Leu Gln Glu Ala Gly Leu Glu Glu Pro Pro Val Gln	
		1300 1305 1310
50	His Ser Ser His Arg Phe Ser Ala Pro Glu Val Pro Ala Glu Val Ala	
	1315	1320 1325
	Lys Val Leu Ala Ser Gly Asn Trp Thr Pro Glu Ser Pro Ser Pro Ala	
55	1330	1335 1340

EP 1 217 066 A1

	Cys Gln Cys Ser Gln Pro Gly Ala Arg Arg Leu Leu Pro Asp Cys Pro	
	1345	1350 1355 1360
5	Ala Ala Ala Gly Gly Pro Pro Pro Pro Gln Ala Val Thr Gly Ser Gly	
		1365 1370 1375
10	Glu Val Val Gln Asn Leu Thr Gly Arg Asn Leu Ser Asp Phe Leu Val	
		1380 1385 1390
	Lys Thr Tyr Pro Arg Leu Val Arg Gln Gly Leu Lys Thr Lys Lys Trp	
		1395 1400 1405
15	Val Asn Glu Val Arg Tyr Gly Gly Phe Ser Leu Gly Gly Arg Asp Pro	
		1410 1415 1420
20	Gly Leu Pro Ser Gly Gln Glu Leu Gly Arg Ser Val Glu Glu Leu Trp	
		1425 1430 1435 1440
	Ala Leu Leu Ser Pro Leu Pro Gly Gly Ala Leu Asp Arg Val Leu Lys	
		1445 1450 1455
25	Asn Leu Thr Ala Trp Ala His Ser Leu Asp Ala Gln Asp Ser Leu Lys	
		1460 1465 1470
30	Ile Trp Phe Asn Asn Lys Gly Trp His Ser Met Val Ala Phe Val Asn	
		1475 1480 1485
	Arg Ala Ser Asn Ala Ile Leu Arg Ala His Leu Pro Pro Gly Arg Ala	
		1490 1495 1500
35	Arg His Ala His Ser Ile Thr Thr Leu Asn His Pro Leu Asn Leu Thr	
		1505 1510 1515 1520
40	Lys Glu Gln Leu Phe Glu Ala Ala Leu Met Ala Ser Ser Val Asp Val	
		1525 1530 1535
	Leu Val Ser Ile Cys Val Val Phe Ala Met Ser Phe Val Pro Ala Ser	
		1540 1545 1550
45	Phe Thr Leu Val Leu Ile Glu Glu Arg Val Thr Arg Ala Lys His Leu	
		1555 1560 1565
50	Gln Leu Met Gly Gly Leu Ser Pro Thr Leu Tyr Trp Leu Gly Asn Phe	
		1570 1575 1580
	Leu Trp Asp Met Cys Asn Tyr Leu Val Pro Ala Cys Ile Val Val Leu	
		1585 1590 1595 1600

EP 1 217 066 A1

	Ile Phe Leu Ala Phe Gln Gln Arg Ala Tyr Val Ala Pro Ala Asn Leu	
	1605	1610 1615
5	Pro Ala Leu Leu Leu Leu Leu Leu Tyr Gly Trp Ser Ile Thr Pro	
	1620	1625 1630
10	Leu Met Tyr Pro Ala Ser Phe Phe Phe Ser Val Pro Ser Thr Ala Tyr	
	1635	1640 1645
	Val Val Leu Thr Cys Ile Asn Leu Phe Ile Gly Ile Asn Gly Ser Met	
15	1650	1655 1660
	Ala Thr Phe Val Leu Glu Leu Phe Ser Asp Gln Lys Leu Gln Glu Val	
	1665	1670 1675 1680
20	Ser Arg Ile Leu Lys Gln Val Phe Leu Ile Phe Pro His Phe Cys Leu	
	1685	1690 1695
	Gly Arg Gly Leu Ile Asp Met Val Arg Asn Gln Ala Met Ala Asp Ala	
25	1700	1705 1710
	Phe Glu Arg Leu Gly Asp Arg Gln Phe Gln Ser Pro Leu Arg Trp Glu	
	1715	1720 1725
30	Val Val Gly Lys Asn Leu Leu Ala Met Val Ile Gln Gly Pro Leu Phe	
	1730	1735 1740
	Leu Leu Phe Thr Leu Leu Leu Gln His Arg Ser Gln Leu Leu Pro Gln	
35	1745	1750 1755 1760
	Pro Arg Val Arg Ser Leu Pro Leu Leu Gly Glu Glu Asp Glu Asp Val	
	1765	1770 1775
40	Ala Arg Glu Arg Glu Arg Val Val Gln Gly Ala Thr Gln Gly Asp Val	
	1780	1785 1790
	Leu Val Leu Arg Asn Leu Thr Lys Val Tyr Arg Gly Gln Arg Met Pro	
45	1795	1800 1805
	Ala Val Asp Arg Leu Cys Leu Gly Ile Pro Pro Gly Glu Cys Phe Gly	
	1810	1815 1820
50	Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Ser Thr Phe Arg Met Val	
	1825	1830 1835 1840
55	Thr Gly Asp Thr Leu Ala Ser Arg Gly Glu Ala Val Leu Ala Gly His	
	1845	1850 1855

EP 1 217 066 A1

Ser Val Ala Arg Glu Pro Ser Ala Ala His Leu Ser Met Gly Tyr Cys
 1860 1865 1870
 5
 Pro Gln Ser Asp Ala Ile Phe Glu Leu Leu Thr Gly Arg Glu His Leu
 1875 1880 1885
 10
 Glu Leu Leu Ala Arg Leu Arg Gly Val Pro Glu Ala Gln Val Ala Gln
 1890 1895 1900
 Thr Ala Gly Ser Gly Leu Ala Arg Leu Gly Leu Ser Trp Tyr Ala Asp
 1905 1910 1915 1920
 15
 Arg Pro Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ala Thr
 1925 1930 1935
 20
 Ala Leu Ala Leu Val Gly Asp Pro Ala Val Val Phe Leu Asp Glu Pro
 1940 1945 1950
 Thr Thr Gly Met Asp Pro Ser Ala Arg Arg Phe Leu Trp Asn Ser Leu
 1955 1960 1965
 25
 Leu Ala Val Val Arg Glu Gly Arg Ser Val Met Leu Thr Ser His Ser
 1970 1975 1980
 30
 Met Glu Glu Cys Glu Ala Leu Cys Ser Arg Leu Ala Ile Met Val Asn
 1985 1990 1995 2000
 Gly Arg Phe Arg Cys Leu Gly Ser Pro Gln His Leu Lys Gly Arg Phe
 2005 2010 2015
 35
 Ala Ala Gly His Thr Leu Thr Leu Arg Val Pro Ala Ala Arg Ser Gln
 2020 2025 2030
 40
 Pro Ala Ala Ala Phe Val Ala Ala Glu Phe Pro Gly Ser Glu Leu Arg
 2035 2040 2045
 Glu Ala His Gly Gly Arg Leu Arg Phe Gln Leu Pro Pro Gly Gly Arg
 2050 2055 2060
 45
 Cys Ala Leu Ala Arg Val Phe Gly Glu Leu Ala Val His Gly Ala Glu
 2065 2070 2075 2080
 50
 His Gly Val Glu Asp Phe Ser Val Ser Gln Thr Met Leu Glu Glu Val
 2085 2090 2095
 Phe Leu Tyr Phe Ser Lys Asp Gln Gly Lys Asp Glu Asp Thr Glu Glu
 2100 2105 2110
 55

EP 1 217 066 A1

Gln Lys Glu Ala Gly Val Gly Val Asp Pro Ala Pro Gly Leu Gln His
2115 2120 2125

5 Pro Lys Arg Val Ser Gln Phe Leu Asp Asp Pro Ser Thr Ala Glu Thr
2130 2135 2140

Val Leu
10 2145

15 <210> 49
<211> 1581
<212> PRT
<213> Homo sapiens

20 <400> 49
Met Arg Lys Arg Lys Ile Ser Val Cys Gln Gln Thr Trp Ala Leu Leu
1 5 10 15

25 Cys Lys Asn Phe Leu Lys Lys Trp Arg Met Lys Arg Glu Ser Leu Met
20 25 30

Glu Trp Leu Asn Ser Leu Leu Leu Leu Leu Cys Leu Tyr Ile Tyr Pro
30 35 40 45

His Ser His Gln Val Asn Asp Phe Ser Ser Leu Leu Thr Met Asp Leu
50 55 60

35 Gly Arg Val Asp Thr Phe Asn Glu Ser Arg Phe Ser Val Val Tyr Thr
65 70 75 80

Pro Val Thr Asn Thr Thr Gln Gln Ile Met Asn Lys Val Ala Ser Thr
40 85 90 95

Pro Phe Leu Ala Gly Lys Glu Val Leu Gly Leu Pro Asp Glu Glu Ser
100 105 110

45 Ile Lys Glu Phe Thr Ala Asn Tyr Pro Glu Glu Ile Val Arg Val Thr
115 120 125

Phe Thr Asn Thr Tyr Ser Tyr His Leu Lys Phe Leu Leu Gly His Gly
50 130 135 140

Met Pro Ala Lys Lys Glu His Lys Asp His Thr Ala His Cys Tyr Glu
145 150 155 160

55 Thr Asn Glu Asp Val Tyr Cys Glu Val Ser Val Phe Trp Lys Glu Gly

EP 1 217 066 A1

	165	170	175
5	Phe Val Ala Leu Gln Ala Ala Ile Asn Ala Ala Ile Ile Glu Ile Thr 180 185 190		
	Thr Asn His Ser Val Met Glu Glu Leu Met Ser Val Thr Gly Lys Asn 195 200 205		
10	Met Lys Met His Ser Phe Ile Gly Gln Ser Gly Val Ile Thr Asp Leu 210 215 220		
15	Tyr Leu Phe Ser Cys Ile Ile Ser Phe Ser Ser Phe Ile Tyr Tyr Ala 225 230 235 240		
	Ser Val Asn Val Thr Arg Glu Arg Lys Arg Met Lys Ala Leu Met Thr 245 250 255		
20	Met Met Gly Leu Arg Asp Ser Ala Phe Trp Leu Ser Trp Gly Leu Leu 260 265 270		
25	Tyr Ala Gly Phe Ile Phe Ile Met Ala Leu Phe Leu Ala Leu Val Ile 275 280 285		
	Arg Ser Thr Gln Phe Ile Ile Leu Ser Gly Phe Met Val Val Phe Ser 290 295 300		
30	Leu Phe Leu Leu Tyr Gly Leu Ser Leu Val Ala Leu Ala Phe Leu Met 305 310 315 320		
35	Ser Ile Leu Val Lys Lys Ser Phe Leu Thr Gly Leu Val Val Phe Leu 325 330 335		
	Leu Thr Val Phe Trp Gly Cys Leu Gly Phe Thr Ser Leu Tyr Arg His 340 345 350		
40	Leu Pro Ala Ser Leu Glu Trp Ile Leu Ser Leu Leu Ser Pro Phe Ala 355 360 365		
45	Phe Met Leu Gly Met Ala Gln Leu Leu His Leu Asp Tyr Asp Leu Asn 370 375 380		
	Ser Asn Ala Phe Pro His Pro Ser Asp Gly Ser Asn Leu Ile Val Ala 385 390 395 400		
50	Thr Asn Phe Met Leu Ala Phe Asp Thr Cys Leu Tyr Leu Ala Leu Ala 405 410 415		
55	Ile Tyr Phe Glu Lys Ile Leu Pro Asn Glu Tyr Gly His Arg Arg Pro		

EP 1 217 066 A1

	420	425	430
5	Pro Leu Phe Phe Leu Lys Ser Ser Phe Trp Ser Gln Thr Gln Lys Thr	435	440 445
10	Asp His Val Ala Leu Glu Asp Glu Met Asp Ala Asp Pro Ser Phe His	450	455 460
15	Asp Ser Phe Glu Gln Ala Pro Pro Glu Phe Gln Gly Lys Glu Ala Ile	465	470 475 480
20	Arg Ile Arg Asn Val Thr Lys Glu Tyr Lys Gly Lys Pro Asp Lys Ile	485	490 495
25	Glu Ala Leu Lys Asp Leu Val Phe Asp Ile Tyr Glu Gly Gln Ile Thr	500	505 510
30	Ala Ile Leu Gly His Ser Gly Ala Gly Lys Ser Thr Leu Leu Asn Ile	515	520 525
35	Leu Ser Gly Leu Ser Val Pro Thr Lys Gly Ser Val Thr Ile Tyr Asn	530	535 540
40	Asn Lys Leu Ser Glu Met Ala Asp Leu Glu Asn Leu Ser Lys Leu Thr	545	550 555 560
45	Gly Val Cys Pro Gln Ser Asn Val Gln Phe Asp Phe Leu Thr Val Arg	565	570 575
50	Glu Asn Leu Arg Leu Phe Ala Lys Ile Lys Gly Ile Leu Pro Gln Glu	580	585 590
55	Val Asp Lys Glu Ile Phe Leu Leu Asp Glu Pro Thr Ala Gly Leu Asp	595	600 605
60	Pro Phe Ser Arg His Gln Val Trp Asn Leu Leu Lys Glu Arg Lys Thr	610	615 620
65	Asp Arg Val Ile Leu Phe Ser Thr Gln Phe Met Asp Glu Ala Asp Ile	625	630 635 640
70	Leu Ala Asp Arg Lys Val Phe Leu Ser Gln Gly Lys Leu Lys Cys Ala	645	650 655
75	Gly Ser Ser Leu Phe Leu Lys Lys Lys Trp Gly Ile Gly Tyr His Leu	660	665 670
80	Ser Leu Gln Leu Asn Glu Ile Cys Val Glu Glu Asn Ile Thr Ser Leu		

EP 1 217 066 A1

	675	680	685
5	Val Lys Gln His Ile Pro Asp Ala Lys Leu Ser Ala Lys Ser Glu Gly 690	695	700
10	Lys Leu Ile Tyr Thr Leu Pro Leu Glu Arg Thr Asn Lys Phe Pro Glu 705	710	715 720
	Leu Tyr Lys Asp Leu Asp Ser Tyr Pro Asp Leu Gly Ile Glu Asn Tyr 725	730	735
15	Gly Val Ser Met Thr Thr Leu Asn Glu Val Phe Leu Lys Leu Glu Gly 740	745	750
20	Lys Ser Thr Ile Asn Glu Ser Asp Ile Ala Ile Leu Gly Glu Val Gln 755	760	765
	Ala Glu Lys Ala Asp Asp Thr Glu Arg Leu Val Glu Met Glu Gln Val 770	775	780
25	Leu Ser Ser Leu Asn Lys Met Arg Lys Thr Ile Gly Gly Val Ala Leu 785	790	795 800
30	Trp Arg Gln Gln Ile Cys Ala Ile Ala Arg Val Arg Leu Leu Lys Leu 805	810	815
	Lys His Glu Arg Lys Ala Leu Leu Ala Leu Leu Leu Ile Leu Met Ala 820	825	830
35	Gly Phe Cys Pro Leu Leu Val Glu Tyr Thr Met Val Lys Ile Tyr Gln 835	840	845
40	Asn Ser Tyr Thr Trp Glu Leu Ser Pro His Leu Tyr Phe Leu Ala Pro 850	855	860
45	Gly Gln Gln Pro His Asp Pro Leu Thr Gln Leu Leu Ile Ile Asn Lys 865	870	875 880
	Thr Gly Ala Ser Ile Asp Asp Phe Ile Gln Ser Val Glu His Gln Asn 885	890	895
50	Ile Ala Leu Glu Val Asp Ala Phe Gly Thr Arg Asn Gly Thr Asp Asp 900	905	910
55	Pro Ser Tyr Asn Gly Ala Ile Thr Val Cys Cys Asn Glu Lys Asn Tyr 915	920	925
	Ser Phe Ser Leu Ala Cys Asn Ala Lys Arg Leu Asn Cys Phe Pro Val		

EP 1 217 066 A1

	930	935	940
5	Leu Met Asp Ile Val Ser Asn Gly Leu Leu Gly Met Val Lys Pro Ser 945	950	955 960
	Val His Ile Arg Thr Glu Arg Ser Thr Phe Leu Glu Asn Gly Gln Asp 965	970	975
10	Asn Pro Ile Gly Phe Leu Ala Tyr Ile Met Phe Trp Leu Val Leu Thr 980	985	990
15	Ser Ser Cys Pro Pro Tyr Ile Ala Met Ser Ser Ile Asp Asp Tyr Lys 995	1000	1005
	Asn Arg Ala Arg Ser Gln Leu Arg Ile Ser Gly Leu Ser Pro Ser Ala 1010	1015	1020
20	Tyr Trp Phe Gly Gln Ala Leu Val Asp Val Ser Leu Tyr Phe Leu Val 1025	1030	1035 1040
25	Phe Val Phe Ile Tyr Leu Met Ser Tyr Ile Ser Asn Phe Glu Asp Met 1045	1050	1055
	Leu Leu Thr Ile Ile His Ile Ile Gln Ile Pro Cys Ala Val Gly Tyr 1060	1065	1070
30	Ser Phe Ser Leu Ile Phe Met Thr Tyr Val Ile Ser Phe Ile Phe Arg 1075	1080	1085
35	Lys Gly Arg Lys Asn Ser Gly Ile Trp Ser Phe Cys Phe Tyr Val Val 1090	1095	1100
	Thr Val Phe Ser Val Ala Gly Phe Ala Phe Ser Ile Phe Glu Ser Asp 1105	1110	1115 1120
40	Ile Pro Phe Ile Phe Thr Phe Leu Ile Pro Pro Ala Thr Met Ile Gly 1125	1130	1135
45	Cys Leu Phe Leu Ser Ser His Leu Leu Phe Ser Ser Leu Phe Ser Glu 1140	1145	1150
	Glu Arg Met Asp Val Gln Pro Phe Leu Val Phe Leu Ile Pro Phe Leu 1155	1160	1165
50	His Phe Ile Ile Phe Leu Phe Thr Leu Arg Cys Leu Glu Trp Lys Phe 1170	1175	1180
55	Gly Lys Lys Ser Met Arg Lys Asp Pro Phe Phe Arg Ile Ser Pro Arg		

EP 1 217 066 A1

	1185		1190		1195		1200
5	Ser Ser Asp Val Cys Gln Asn Pro Glu Glu Pro Glu Gly Glu Asp Glu	1205		1210		1215	
10	Asp Val Gln Met Glu Arg Val Arg Thr Ala Asn Ala Leu Asn Ser Thr	1220		1225		1230	
	Asn Phe Asp Glu Lys Pro Val Ile Ile Ala Ser Cys Leu Arg Lys Glu	1235		1240		1245	
15	Tyr Ala Gly Lys Arg Lys Gly Cys Phe Ser Lys Arg Lys Asn Lys Ile	1250		1255		1260	
20	Ala Thr Arg Asn Val Ser Phe Cys Val Arg Lys Gly Glu Val Leu Gly	1265		1270		1275	1280
	Leu Leu Gly His Asn Gly Ala Gly Lys Ser Thr Ser Ile Lys Val Ile	1285		1290		1295	
25	Thr Gly Asp Thr Lys Pro Thr Ala Gly Gln Val Leu Leu Lys Gly Ser	1300		1305		1310	
30	Gly Gly Gly Asp Ala Leu Glu Phe Leu Gly Tyr Cys Pro Gln Glu Asn	1315		1320		1325	
	Ala Leu Trp Pro Asn Leu Thr Val Arg Gln His Leu Glu Val Tyr Ala	1330		1335		1340	
35	Ala Val Lys Gly Leu Arg Lys Gly Asp Ala Glu Val Ala Ile Thr Arg	1345		1350		1355	1360
40	Leu Val Asp Ala Leu Lys Leu Gln Asp Gln Leu Lys Ser Pro Val Lys	1365		1370		1375	
	Thr Leu Ser Glu Gly Ile Lys Arg Lys Leu Cys Phe Val Leu Ser Ile	1380		1385		1390	
45	Leu Gly Asn Pro Ser Val Val Leu Leu Asp Glu Pro Ser Thr Gly Met	1395		1400		1405	
50	Asp Pro Glu Gly Gln Gln Gln Met Trp Gln Ala Ile Arg Ala Thr Phe	1410		1415		1420	
	Arg Asn Thr Glu Arg Gly Ala Leu Leu Thr Thr His Tyr Met Ala Glu	1425		1430		1435	1440
55	Ala Glu Ala Val Cys Asp Arg Val Ala Ile Met Val Ser Gly Arg Leu						

EP 1 217 066 A1

	1445	1450	1455
5	Arg Cys Ile Gly Ser Ile Gln His Leu Lys Ser Lys Phe Gly Lys Asp		
	1460	1465	1470
10	Tyr Leu Leu Glu Met Lys Val Lys Asn Leu Ala Gln Val Glu Pro Leu		
	1475	1480	1485
15	His Ala Glu Ile Leu Arg Leu Phe Pro Gln Ala Ala Arg Gln Glu Arg		
	1490	1495	1500
20	Tyr Ser Ser Leu Met Val Tyr Lys Leu Pro Val Glu Asp Val Gln Pro		
	1505	1510	1515
	Leu Ala Gln Ala Phe Phe Lys Leu Glu Lys Val Lys Gln Ser Phe Asp		
	1525	1530	1535
25	Leu Glu Glu Tyr Ser Leu Ser Gln Ser Thr Leu Glu Gln Val Phe Leu		
	1540	1545	1550
30	Glu Leu Ser Lys Glu Gln Glu Leu Gly Asp Phe Glu Glu Asp Phe Asp		
	1555	1560	1565
	Pro Ser Val Lys Trp Lys Leu Leu Pro Gln Glu Glu Pro		
	1570	1575	1580
35	<210> 50		
	<211> 1279		
	<212> PRT		
	<213> Homo sapiens		
40	<400> 50		
	Met Asp Leu Glu Gly Asp Arg Asn Gly Gly Ala Lys Lys Lys Asn Phe		
	1	5	10
45	Phe Lys Leu Asn Asn Lys Ser Glu Lys Asp Lys Lys Glu Lys Lys Pro		
	20	25	30
50	Thr Val Ser Val Phe Ser Met Phe Arg Tyr Ser Asn Trp Leu Asp Lys		
	35	40	45
55	Leu Tyr Met Val Val Gly Thr Leu Ala Ala Ile Ile His Gly Ala Gly		
	50	55	60
	Leu Pro Leu Met Met Leu Val Phe Gly Glu Met Thr Asp Ile Phe Ala		
	65	70	75
			80

EP 1 217 066 A1

5	Asn Ala Gly Asn Leu Glu Asp Leu Met Ser Asn Ile Thr Asn Arg Ser	85	90	95
	Asp Ile Asn Asp Thr Gly Phe Phe Met Asn Leu Glu Glu Asp Met Thr	100	105	110
10	Arg Tyr Ala Tyr Tyr Tyr Ser Gly Ile Gly Ala Gly Val Leu Val Ala	115	120	125
15	Ala Tyr Ile Gln Val Ser Phe Trp Cys Leu Ala Ala Gly Arg Gln Ile	130	135	140
	His Lys Ile Arg Lys Gln Phe Phe His Ala Ile Met Arg Gln Glu Ile	145	150	155
20	Gly Trp Phe Asp Val His Asp Val Gly Glu Leu Asn Thr Arg Leu Thr	165	170	175
25	Asp Asp Val Ser Lys Ile Asn Glu Gly Ile Gly Asp Lys Ile Gly Met	180	185	190
	Phe Phe Gln Ser Met Ala Thr Phe Phe Thr Gly Phe Ile Val Gly Phe	195	200	205
30	Thr Arg Gly Trp Lys Leu Thr Leu Val Ile Leu Ala Ile Ser Pro Val	210	215	220
35	Leu Gly Leu Ser Ala Ala Val Trp Ala Lys Ile Leu Ser Ser Phe Thr	225	230	235
	Asp Lys Glu Leu Leu Ala Tyr Ala Lys Ala Gly Ala Val Ala Glu Glu	245	250	255
40	Val Leu Ala Ala Ile Arg Thr Val Ile Ala Phe Gly Gly Gln Lys Lys	260	265	270
45	Glu Leu Glu Arg Tyr Asn Lys Asn Leu Glu Glu Ala Lys Arg Ile Gly	275	280	285
	Ile Lys Lys Ala Ile Thr Ala Asn Ile Ser Ile Gly Ala Ala Phe Leu	290	295	300
50	Leu Ile Tyr Ala Ser Tyr Ala Leu Ala Phe Trp Tyr Gly Thr Thr Leu	305	310	315
55	Val Leu Ser Gly Glu Tyr Ser Ile Gly Gln Val Leu Thr Val Phe Ser	325	330	335

EP 1 217 066 A1

	Val	Leu	Ile	Gly	Ala	Phe	Ser	Val	Gly	Gln	Ala	Ser	Pro	Ser	Ile	Glu	
				340					345					350			
5																	
	Ala	Phe	Ala	Asn	Ala	Arg	Gly	Ala	Ala	Tyr	Glu	Ile	Phe	Lys	Ile	Ile	
				355				360					365				
10	Asp	Asn	Lys	Pro	Ser	Ile	Asp	Ser	Tyr	Ser	Lys	Ser	Gly	His	Lys	Pro	
				370				375					380				
	Asp	Asn	Ile	Lys	Gly	Asn	Leu	Glu	Phe	Arg	Asn	Val	His	Phe	Ser	Tyr	
15				385			390				395					400	
	Pro	Ser	Arg	Lys	Glu	Val	Lys	Ile	Leu	Lys	Gly	Leu	Asn	Leu	Lys	Val	
					405					410				415			
20	Gln	Ser	Gly	Gln	Thr	Val	Ala	Leu	Val	Gly	Asn	Ser	Gly	Cys	Gly	Lys	
				420					425					430			
	Ser	Thr	Thr	Val	Gln	Leu	Met	Gln	Arg	Leu	Tyr	Asp	Pro	Thr	Glu	Gly	
25				435				440					445				
	Met	Val	Ser	Val	Asp	Gly	Gln	Asp	Ile	Arg	Thr	Ile	Asn	Val	Arg	Phe	
				450			455					460					
30	Leu	Arg	Glu	Ile	Ile	Gly	Val	Val	Ser	Gln	Glu	Pro	Val	Leu	Phe	Ala	
				465			470				475					480	
	Thr	Thr	Ile	Ala	Glu	Asn	Ile	Arg	Tyr	Gly	Arg	Glu	Asn	Val	Thr	Met	
35					485					490					495		
	Asp	Glu	Ile	Glu	Lys	Ala	Val	Lys	Glu	Ala	Asn	Ala	Tyr	Asp	Phe	Ile	
				500					505					510			
40	Met	Lys	Leu	Pro	His	Lys	Phe	Asp	Thr	Leu	Val	Gly	Glu	Arg	Gly	Ala	
				515				520					525				
	Gln	Leu	Ser	Gly	Gly	Gln	Lys	Gln	Arg	Ile	Ala	Ile	Ala	Arg	Ala	Leu	
45				530			535					540					
	Val	Arg	Asn	Pro	Lys	Ile	Leu	Leu	Leu	Asp	Glu	Ala	Thr	Ser	Ala	Leu	
				545			550				555					560	
50																	
	Asp	Thr	Glu	Ser	Glu	Ala	Val	Val	Gln	Val	Ala	Leu	Asp	Lys	Ala	Arg	
					565				570					575			
55	Lys	Gly	Arg	Thr	Thr	Ile	Val	Ile	Ala	His	Arg	Leu	Ser	Thr	Val	Arg	
				580				585						590			

EP 1 217 066 A1

5 Asn Ala Asp Val Ile Ala Gly Phe Asp Asp Gly Val Ile Val Glu Lys
 595 600 605
 Gly Asn His Asp Glu Leu Met Lys Glu Lys Gly Ile Tyr Phe Lys Leu
 610 615 620
 10 Val Thr Met Gln Thr Ala Gly Asn Glu Val Glu Leu Glu Asn Ala Ala
 625 630 635 640
 Asp Glu Ser Lys Ser Glu Ile Asp Ala Leu Glu Met Ser Ser Asn Asp
 15 645 650 655
 Ser Arg Ser Ser Leu Ile Arg Lys Arg Ser Thr Arg Arg Ser Val Arg
 660 665 670
 20 Gly Ser Gln Ala Gln Asp Arg Lys Leu Ser Thr Lys Glu Ala Leu Asp
 675 680 685
 Glu Ser Ile Pro Pro Val Ser Phe Trp Arg Ile Met Lys Leu Asn Leu
 25 690 695 700
 Thr Glu Trp Pro Tyr Phe Val Val Gly Val Phe Cys Ala Ile Ile Asn
 705 710 715 720
 30 Gly Gly Leu Gln Pro Ala Phe Ala Ile Ile Phe Ser Lys Ile Ile Gly
 725 730 735
 Val Phe Thr Arg Ile Asp Asp Pro Glu Thr Lys Arg Gln Asn Ser Asn
 35 740 745 750
 Leu Phe Ser Leu Leu Phe Leu Ala Leu Gly Ile Ile Ser Phe Ile Thr
 755 760 765
 40 Phe Phe Leu Gln Gly Phe Thr Phe Gly Lys Ala Gly Glu Ile Leu Thr
 770 775 780
 Lys Arg Leu Arg Tyr Met Val Phe Arg Ser Met Leu Arg Gln Asp Val
 45 785 790 795 800
 Ser Trp Phe Asp Asp Pro Lys Asn Thr Thr Gly Ala Leu Thr Thr Arg
 50 805 810 815
 Leu Ala Asn Asp Ala Ala Gln Val Lys Gly Ala Ile Gly Ser Arg Leu
 820 825 830
 55 Ala Val Ile Thr Gln Asn Ile Ala Asn Leu Gly Thr Gly Ile Ile Ile
 835 840 845

EP 1 217 066 A1

5	Ser Phe Ile Tyr Gly Trp Gln Leu Thr Leu Leu Leu Leu Ala Ile Val	850	855	860
10	Pro Ile Ile Ala Ile Ala Gly Val Val Glu Met Lys Met Leu Ser Gly	865	870	875
				880
15	Gln Ala Leu Lys Asp Lys Lys Glu Leu Glu Gly Ser Gly Lys Ile Ala	885	890	895
	Thr Glu Ala Ile Glu Asn Phe Arg Thr Val Val Ser Leu Thr Gln Glu	900	905	910
20	Gln Lys Phe Glu His Met Tyr Ala Gln Ser Leu Gln Val Pro Tyr Arg	915	920	925
	Asn Ser Leu Arg Lys Ala His Ile Phe Gly Ile Thr Phe Ser Phe Thr	930	935	940
25	Gln Ala Met Met Tyr Phe Ser Tyr Ala Gly Cys Phe Arg Phe Gly Ala	945	950	955
				960
30	Tyr Leu Val Ala His Lys Leu Met Ser Phe Glu Asp Val Leu Leu Val	965	970	975
	Phe Ser Ala Val Val Phe Gly Ala Met Ala Val Gly Gln Val Ser Ser	980	985	990
35	Phe Ala Pro Asp Tyr Ala Lys Ala Lys Ile Ser Ala Ala His Ile Ile	995	1000	1005
40	Met Ile Ile Glu Lys Thr Pro Leu Ile Asp Ser Tyr Ser Thr Glu Gly	1010	1015	1020
	Leu Met Pro Asn Thr Leu Glu Gly Asn Val Thr Phe Gly Glu Val Val	1025	1030	1035
				1040
45	Phe Asn Tyr Pro Thr Arg Pro Asp Ile Pro Val Leu Gln Gly Leu Ser	1045	1050	1055
50	Leu Glu Val Lys Lys Gly Gln Thr Leu Ala Leu Val Gly Ser Ser Gly	1060	1065	1070
	Cys Gly Lys Ser Thr Val Val Gln Leu Leu Glu Arg Phe Tyr Asp Pro	1075	1080	1085
55	Leu Ala Gly Lys Val Leu Leu Asp Gly Lys Glu Ile Lys Arg Leu Asn	1090	1095	1100

EP 1 217 066 A1

5 Val Gln Trp Leu Arg Ala His Leu Gly Ile Val Ser Gln Glu Pro Ile
 1105 1110 1115 1120
 Leu Phe Asp Cys Ser Ile Ala Glu Asn Ile Ala Tyr Gly Asp Asn Ser
 1125 1130 1135
 10 Arg Val Val Ser Gln Glu Glu Ile Val Arg Ala Ala Lys Glu Ala Asn
 1140 1145 1150
 Ile His Ala Phe Ile Glu Ser Leu Pro Asn Lys Tyr Ser Thr Lys Val
 15 1155 1160 1165
 Gly Asp Lys Gly Thr Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile Ala
 1170 1175 1180
 20 Ile Ala Arg Ala Leu Val Arg Gln Pro His Ile Leu Leu Leu Asp Glu
 1185 1190 1195 1200
 Ala Thr Ser Ala Leu Asp Thr Glu Ser Glu Lys Val Val Gln Glu Ala
 25 1205 1210 1215
 Leu Asp Lys Ala Arg Glu Gly Arg Thr Cys Ile Val Ile Ala His Arg
 1220 1225 1230
 30 Leu Ser Thr Ile Gln Asn Ala Asp Leu Ile Val Val Phe Gln Asn Gly
 1235 1240 1245
 Arg Val Lys Glu His Gly Thr His Gln Gln Leu Leu Ala Gln Lys Gly
 35 1250 1255 1260
 Ile Tyr Phe Ser Met Val Ser Val Gln Ala Gly Thr Lys Arg Gln
 40 1265 1270 1275
 <210> 51
 <211> 808
 45 <212> PRT
 <213> Homo sapiens
 <400> 51
 50 Met Ala Glu Leu Leu Ala Ser Ala Gly Ser Ala Cys Ser Trp Asp Phe
 1 5 10 15
 Pro Arg Ala Pro Pro Ser Phe Pro Pro Pro Ala Ala Ser Arg Gly Gly
 55 20 25 30

EP 1 217 066 A1

	Leu Gly Gly Thr Arg Ser Phe Arg Pro His Arg Gly Ala Glu Ser Pro	
	35 40 45	
5	Arg Pro Gly Arg Asp Arg Asp Gly Val Arg Val Pro Met Ala Ser Ser	
	50 55 60	
10	Arg Cys Pro Ala Pro Arg Gly Cys Arg Cys Leu Pro Gly Ala Ser Leu	
	65 70 75 80	
	Ala Trp Leu Gly Thr Val Leu Leu Leu Leu Ala Asp Trp Val Leu Leu	
	85 90 95	
15	Arg Thr Ala Leu Pro Arg Ile Phe Ser Leu Leu Val Pro Thr Ala Leu	
	100 105 110	
20	Pro Leu Leu Arg Val Trp Ala Val Gly Leu Ser Arg Trp Ala Val Leu	
	115 120 125	
	Trp Leu Gly Ala Cys Gly Val Leu Arg Ala Thr Val Gly Ser Lys Ser	
	130 135 140	
25	Glu Asn Ala Gly Ala Gln Gly Trp Leu Ala Ala Leu Lys Pro Leu Ala	
	145 150 155 160	
30	Ala Ala Leu Gly Leu Ala Leu Pro Gly Leu Ala Leu Phe Arg Glu Leu	
	165 170 175	
	Ile Ser Trp Gly Ala Pro Gly Ser Ala Asp Ser Thr Arg Leu Leu His	
	180 185 190	
35	Trp Gly Ser His Pro Thr Ala Phe Val Val Ser Tyr Ala Ala Ala Leu	
	195 200 205	
40	Pro Ala Ala Ala Leu Trp His Lys Leu Gly Ser Leu Trp Val Pro Gly	
	210 215 220	
45	Gly Gln Gly Gly Ser Gly Asn Pro Val Arg Arg Leu Leu Gly Cys Leu	
	225 230 235 240	
	Gly Ser Glu Thr Arg Arg Leu Ser Leu Phe Leu Val Leu Val Val Leu	
	245 250 255	
50	Ser Ser Leu Gly Glu Met Ala Ile Pro Phe Phe Thr Gly Arg Leu Thr	
	260 265 270	
55	Asp Trp Ile Leu Gln Asp Gly Ser Ala Asp Thr Phe Thr Arg Asn Leu	
	275 280 285	

EP 1 217 066 A1

	Thr	Leu	Met	Ser	Ile	Leu	Thr	Ile	Ala	Ser	Ala	Val	Leu	Glu	Phe	Val	
	290						295						300				
5	Gly	Asp	Gly	Ile	Tyr	Asn	Asn	Thr	Met	Gly	His	Val	His	Ser	His	Leu	
	305					310				315						320	
	Gln	Gly	Glu	Val	Phe	Gly	Ala	Val	Leu	Arg	Gln	Glu	Thr	Glu	Phe	Phe	
10					325					330					335		
	Gln	Gln	Asn	Gln	Thr	Gly	Asn	Ile	Met	Ser	Arg	Val	Thr	Glu	Asp	Thr	
				340					345					350			
15	Ser	Thr	Leu	Ser	Asp	Ser	Leu	Ser	Glu	Asn	Leu	Ser	Leu	Phe	Leu	Trp	
		355						360					365				
	Tyr	Leu	Val	Arg	Gly	Leu	Cys	Leu	Leu	Gly	Ile	Met	Leu	Trp	Gly	Ser	
20		370					375					380					
	Val	Ser	Leu	Thr	Met	Val	Thr	Leu	Ile	Thr	Leu	Pro	Leu	Leu	Phe	Leu	
	385					390					395					400	
25	Leu	Pro	Lys	Lys	Val	Gly	Lys	Trp	Tyr	Gln	Leu	Leu	Glu	Val	Gln	Val	
					405					410					415		
	Arg	Glu	Ser	Leu	Ala	Lys	Ser	Ser	Gln	Val	Ala	Ile	Glu	Ala	Leu	Ser	
30				420					425					430			
	Ala	Met	Pro	Thr	Val	Arg	Ser	Phe	Ala	Asn	Glu	Glu	Gly	Glu	Ala	Gln	
		435						440					445				
35	Lys	Phe	Arg	Glu	Lys	Leu	Gln	Glu	Ile	Lys	Thr	Leu	Asn	Gln	Lys	Glu	
	450						455					460					
	Ala	Val	Ala	Tyr	Ala	Val	Asn	Ser	Trp	Thr	Thr	Ser	Ile	Ser	Gly	Met	
40		465				470					475				480		
	Leu	Leu	Lys	Val	Gly	Ile	Leu	Tyr	Ile	Gly	Gly	Gln	Leu	Val	Thr	Ser	
45				485						490					495		
	Gly	Ala	Val	Ser	Ser	Gly	Asn	Leu	Val	Thr	Phe	Val	Leu	Tyr	Gln	Met	
				500					505					510			
50	Gln	Phe	Thr	Gln	Ala	Val	Glu	Val	Leu	Leu	Ser	Ile	Tyr	Pro	Arg	Val	
		515						520					525				
	Gln	Lys	Ala	Val	Gly	Ser	Ser	Glu	Lys	Ile	Phe	Glu	Tyr	Leu	Asp	Arg	
55		530					535					540					

EP 1 217 066 A1

	Thr	Pro	Arg	Cys	Pro	Pro	Ser	Gly	Leu	Leu	Thr	Pro	Leu	His	Leu	Glu	
	545					550					555					560	
5	Gly	Leu	Val	Gln	Phe	Gln	Asp	Val	Ser	Phe	Ala	Tyr	Pro	Asn	Arg	Pro	
				565						570					575		
	Asp	Val	Leu	Val	Leu	Gln	Gly	Leu	Thr	Phe	Thr	Leu	Arg	Pro	Gly	Glu	
10				580				585						590			
	Val	Thr	Ala	Leu	Val	Gly	Pro	Asn	Gly	Ser	Gly	Lys	Ser	Thr	Val	Ala	
			595					600						605			
15	Ala	Leu	Leu	Gln	Asn	Leu	Tyr	Gln	Pro	Thr	Gly	Gly	Gln	Leu	Leu	Leu	
	610						615					620					
	Asp	Gly	Lys	Pro	Leu	Pro	Gln	Tyr	Glu	His	Arg	Tyr	Leu	His	Arg	Gln	
20	625					630					635					640	
	Val	Ala	Ala	Val	Gly	Gln	Glu	Pro	Gln	Val	Phe	Gly	Arg	Ser	Leu	Gln	
				645						650					655		
25	Glu	Asn	Ile	Ala	Tyr	Gly	Leu	Thr	Gln	Lys	Pro	Thr	Met	Glu	Glu	Ile	
				660					665					670			
	Thr	Ala	Ala	Ala	Val	Lys	Ser	Gly	Ala	His	Ser	Phe	Ile	Ser	Gly	Leu	
30				675				680						685			
	Pro	Gln	Gly	Tyr	Asp	Thr	Glu	Val	Asp	Glu	Ala	Gly	Ser	Gln	Leu	Ser	
		690					695					700					
35	Gly	Gly	Gln	Arg	Gln	Ala	Val	Ala	Leu	Ala	Arg	Ala	Leu	Ile	Arg	Lys	
	705				710						715				720		
	Pro	Cys	Val	Leu	Ile	Leu	Asp	Asp	Ala	Thr	Ser	Ala	Leu	Asp	Ala	Asn	
40				725						730				735			
	Ser	Gln	Leu	Gln	Val	Glu	Gln	Leu	Leu	Tyr	Glu	Ser	Pro	Glu	Arg	Tyr	
45				740				745						750			
	Ser	Arg	Ser	Val	Leu	Leu	Ile	Thr	Gln	His	Leu	Ser	Leu	Val	Glu	Gln	
				755				760						765			
50	Ala	Asp	His	Ile	Leu	Phe	Leu	Glu	Gly	Gly	Ala	Ile	Arg	Glu	Gly	Gly	
		770					775						780				
	Thr	His	Gln	Gln	Leu	Met	Glu	Lys	Lys	Gly	Cys	Tyr	Trp	Ala	Met	Val	
55	785					790					795					800	

EP 1 217 066 A1

Gln Ala Pro Ala Asp Ala Pro Glu
805

5

<210> 52

<211> 808

10

<212> PRT

<213> Homo sapiens

<400> 52

15

Met Ala Glu Leu Leu Ala Ser Ala Gly Ser Ala Cys Ser Trp Asp Phe
1 5 10 15

Pro Arg Ala Pro Pro Ser Phe Pro Pro Pro Ala Ala Ser Arg Gly Gly
20 25 30

20

Leu Gly Gly Thr Arg Ser Phe Arg Pro His Arg Gly Ala Glu Ser Pro
35 40 45

25

Arg Pro Gly Arg Asp Arg Asp Gly Val Arg Val Pro Met Ala Ser Ser
50 55 60

30

Arg Cys Pro Ala Pro Arg Gly Cys Arg Cys Leu Pro Gly Ala Ser Leu
65 70 75 80

Ala Trp Leu Gly Thr Val Leu Leu Leu Leu Ala Asp Trp Val Leu Leu
85 90 95

35

Arg Thr Ala Leu Pro Arg Ile Phe Ser Leu Leu Val Pro Thr Ala Leu
100 105 110

40

Pro Leu Leu Arg Val Trp Ala Val Gly Leu Ser Arg Trp Ala Val Leu
115 120 125

Trp Leu Gly Ala Cys Gly Val Leu Arg Ala Thr Val Gly Ser Lys Ser
130 135 140

45

Glu Asn Ala Gly Ala Gln Gly Trp Leu Ala Ala Leu Lys Pro Leu Ala
145 150 155 160

50

Ala Ala Leu Gly Leu Ala Leu Pro Gly Leu Ala Leu Phe Arg Glu Leu
165 170 175

Ile Ser Trp Gly Ala Pro Gly Ser Ala Asp Ser Thr Arg Leu Leu His
180 185 190

55

Trp Gly Ser His Pro Thr Ala Phe Val Val Ser Tyr Ala Ala Ala Leu

EP 1 217 066 A1

	195	200	205
5	Pro Ala Ala Ala Leu Trp His Lys Leu Gly Ser Leu Trp Val Pro Gly 210 215 220		
10	Gly Gln Gly Gly Ser Gly Asn Pro Val Arg Arg Leu Leu Gly Cys Leu 225 230 235 240		
	Gly Ser Glu Thr Arg Arg Leu Ser Leu Phe Leu Val Leu Val Val Leu 245 250 255		
15	Ser Ser Leu Gly Glu Met Ala Ile Pro Phe Phe Thr Gly Arg Leu Thr 260 265 270		
20	Asp Trp Ile Leu Gln Asp Gly Ser Ala Asp Thr Phe Thr Arg Asn Leu 275 280 285		
	Thr Leu Met Ser Ile Leu Thr Ile Ala Ser Ala Val Leu Glu Phe Val 290 295 300		
25	Gly Asp Gly Ile Tyr Asn Asn Thr Met Gly His Val His Ser His Leu 305 310 315 320		
30	Gln Gly Glu Val Phe Gly Ala Val Leu Arg Gln Glu Thr Glu Phe Phe 325 330 335		
	Gln Gln Asn Gln Thr Gly Asn Ile Met Ser Arg Val Thr Glu Asp Thr 340 345 350		
35	Ser Thr Leu Ser Asp Ser Leu Ser Glu Asn Leu Ser Leu Phe Leu Trp 355 360 365		
40	Tyr Leu Val Arg Gly Leu Cys Leu Leu Gly Ile Met Leu Trp Gly Ser 370 375 380		
	Val Ser Leu Thr Met Val Thr Leu Ile Thr Leu Pro Leu Leu Phe Leu 385 390 395 400		
45	Leu Pro Lys Lys Val Gly Lys Trp Tyr Gln Leu Leu Glu Val Gln Val 405 410 415		
50	Arg Glu Ser Leu Ala Lys Ser Ser Gln Val Ala Ile Glu Ala Leu Ser 420 425 430		
	Ala Met Pro Thr Val Arg Ser Phe Ala Asn Glu Glu Gly Glu Ala Gln 435 440 445		
55	Lys Phe Arg Glu Lys Leu Gln Glu Ile Lys Thr Leu Asn Gln Lys Glu		

EP 1 217 066 A1

	450		455		460	
5	Ala Val Ala Tyr Ala Val Asn Ser Trp Thr Thr Ser Ile Ser Gly Met					
	465		470		475	480
	Leu Leu Lys Val Gly Ile Leu Tyr Ile Gly Gly Gln Leu Val Thr Ser					
		485		490		495
10	Gly Ala Val Ser Ser Gly Asn Leu Val Thr Phe Val Leu Tyr Gln Met					
		500		505		510
15	Gln Phe Thr Gln Ala Val Glu Val Leu Leu Ser Ile Tyr Pro Arg Val					
		515		520		525
	Gln Lys Ala Val Gly Ser Ser Glu Lys Ile Phe Glu Tyr Leu Asp Arg					
20		530		535		540
	Thr Pro Arg Cys Pro Pro Ser Gly Leu Leu Thr Pro Leu His Leu Glu					
	545		550		555	560
25	Gly Leu Val Gln Phe Gln Asp Val Ser Phe Ala Tyr Pro Asn Arg Pro					
		565		570		575
	Asp Val Leu Val Leu Gln Gly Leu Thr Phe Thr Leu Arg Pro Gly Glu					
30		580		585		590
	Val Thr Ala Leu Val Gly Pro Asn Gly Ser Gly Lys Ser Thr Val Ala					
		595		600		605
35	Ala Leu Leu Gln Asn Leu Tyr Gln Pro Thr Gly Gly Gln Leu Leu Leu					
	610		615		620	
	Asp Gly Lys Pro Leu Pro Gln Tyr Glu His Arg Tyr Leu His Arg Gln					
40	625		630		635	640
	Val Ala Ala Val Gly Gln Glu Pro Gln Val Phe Gly Arg Ser Leu Gln					
		645		650		655
45	Glu Asn Ile Ala Tyr Gly Leu Thr Gln Lys Pro Thr Met Glu Glu Ile					
		660		665		670
	Thr Ala Ala Ala Val Lys Ser Gly Ala His Ser Phe Ile Ser Gly Leu					
50		675		680		685
	Pro Gln Gly Tyr Asp Thr Glu Val Asp Glu Ala Gly Ser Gln Leu Ser					
		690		695		700
55	Gly Gly Gln Arg Gln Ala Val Ala Leu Ala Arg Ala Leu Ile Arg Lys					

```

705              710              715              720

Pro Cys Val Leu Ile Leu Asp Asp Ala Thr Ser Ala Leu Asp Ala Asn
5              725              730              735

Ser Gln Leu Gln Val Glu Gln Leu Leu Tyr Glu Ser Pro Glu Arg Tyr
              740              745              750

10 Ser Arg Ser Val Leu Leu Ile Thr Gln His Leu Ser Leu Val Glu Gln
              755              760              765

15 Ala Asp His Ile Leu Phe Leu Glu Gly Gly Ala Ile Arg Glu Gly Gly
              770              775              780

Thr His Gln Gln Leu Met Glu Lys Lys Gly Cys Tyr Trp Ala Met Val
20 785              790              795              800

Gln Ala Pro Ala Asp Ala Pro Glu
              805

25

<210> 53
<211> 1232
30 <212> PRT
<213> Homo sapiens

<400> 53
Met Asp Leu Glu Ala Ala Lys Asn Gly Thr Ala Trp Arg Pro Thr Ser
35 1              5              10              15

Ala Glu Gly Asp Phe Glu Leu Gly Ile Ser Ser Lys Gln Lys Arg Lys
40 20              25              30

Lys Thr Lys Thr Val Lys Met Ile Gly Val Leu Thr Leu Phe Arg Tyr
35              40              45

45 Ser Asp Trp Gln Asp Lys Leu Phe Met Ser Leu Gly Thr Ile Met Ala
50 50              55              60

Ile Ala His Gly Ser Gly Leu Pro Leu Met Met Ile Val Phe Gly Glu
55 65              70              75              80

Met Thr Asp Lys Phe Val Asp Thr Ala Gly Asn Phe Ser Phe Pro Val
85              90              95

Asn Phe Ser Leu Ser Leu Leu Asn Pro Gly Lys Ile Leu Glu Glu Glu
100              105              110

```

EP 1 217 066 A1

5	Met Thr Arg Tyr Ala Tyr Tyr Tyr Ser Gly Leu Gly Ala Gly Val Leu	115	120	125
	Val Ala Ala Tyr Ile Gln Val Ser Phe Trp Thr Leu Ala Ala Gly Arg	130	135	140
10	Gln Ile Arg Lys Ile Arg Gln Lys Phe Phe His Ala Ile Leu Arg Gln	145	150	155
				160
15	Glu Ile Gly Trp Phe Asp Ile Asn Asp Thr Thr Glu Leu Asn Thr Arg	165	170	175
	Leu Thr Asp Asp Ile Ser Lys Ile Ser Glu Gly Ile Gly Asp Lys Val	180	185	190
20	Gly Met Phe Phe Gln Ala Val Ala Thr Phe Phe Ala Gly Phe Ile Val	195	200	205
25	Gly Phe Ile Arg Gly Trp Lys Leu Thr Leu Val Ile Met Ala Ile Ser	210	215	220
	Pro Ile Leu Gly Leu Ser Ala Ala Val Trp Ala Lys Ile Leu Ser Ala	225	230	235
30				240
	Phe Ser Asp Lys Glu Leu Ala Ala Tyr Ala Lys Ala Gly Ala Val Ala	245	250	255
35	Glu Glu Ala Leu Gly Ala Ile Arg Thr Val Ile Ala Phe Gly Gly Gln	260	265	270
	Asn Lys Glu Leu Glu Arg Tyr Gln Lys His Leu Glu Asn Ala Lys Glu	275	280	285
40	Ile Gly Ile Lys Lys Ala Ile Ser Ala Asn Ile Ser Met Gly Ile Ala	290	295	300
45	Phe Leu Leu Ile Tyr Ala Ser Tyr Ala Leu Ala Phe Trp Tyr Gly Ser	305	310	315
				320
50	Thr Leu Val Ile Ser Lys Glu Tyr Thr Ile Gly Asn Ala Met Thr Val	325	330	335
	Phe Phe Ser Ile Leu Ile Gly Ala Phe Ser Val Gly Gln Ala Ala Pro	340	345	350
55	Cys Ile Asp Ala Phe Ala Asn Ala Arg Gly Ala Ala Tyr Val Ile Phe	355	360	365

EP 1 217 066 A1

5 Asp Ile Ile Asp Asn Asn Pro Lys Ile Asp Ser Phe Ser Glu Arg Gly
 370 375 380
 His Lys Pro Asp Ser Ile Lys Gly Asn Leu Glu Phe Asn Asp Val His
 385 390 395 400
 10 Phe Ser Tyr Pro Ser Arg Ala Asn Val Lys Ile Leu Lys Gly Leu Asn
 405 410 415
 Leu Lys Val Gln Ser Gly Gln Thr Val Ala Leu Val Gly Ser Ser Gly
 15 420 425 430
 Cys Gly Lys Ser Thr Thr Val Gln Leu Ile Gln Arg Leu Tyr Asp Pro
 435 440 445
 20 Asp Glu Gly Thr Ile Asn Ile Asp Gly Gln Asp Ile Arg Asn Phe Asn
 450 455 460
 Val Asn Tyr Leu Arg Glu Ile Ile Gly Val Val Ser Gln Glu Pro Val
 25 465 470 475 480
 Leu Phe Ser Thr Thr Ile Ala Glu Asn Ile Cys Tyr Gly Arg Gly Asn
 485 490 495
 30 Val Thr Met Asp Glu Ile Lys Lys Ala Val Lys Glu Ala Asn Ala Tyr
 500 505 510
 Glu Phe Ile Met Lys Leu Pro Gln Lys Phe Asp Thr Leu Val Gly Glu
 35 515 520 525
 Arg Gly Ala Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala
 530 535 540
 40 Arg Ala Leu Val Arg Asn Pro Lys Ile Leu Leu Leu Asp Glu Ala Thr
 545 550 555 560
 Ser Ala Leu Asp Thr Glu Ser Glu Ala Glu Val Gln Ala Ala Leu Asp
 45 565 570 575
 Lys Ala Arg Glu Gly Arg Thr Thr Ile Val Ile Ala His Arg Leu Ser
 50 580 585 590
 Thr Val Arg Asn Ala Asp Val Ile Ala Gly Phe Glu Asp Gly Val Ile
 595 600 605
 55 Val Glu Gln Gly Ser His Ser Glu Leu Met Lys Lys Glu Gly Val Tyr
 610 615 620

EP 1 217 066 A1

5	Phe Lys Leu Val Asn Met Gln Thr Ser Gly Ser Gln Ile Gln Ser Glu	625	630	635	640
	Glu Phe Glu Leu Asn Asp Glu Lys Ala Ala Thr Arg Met Ala Pro Asn	645	650	655	
10	Gly Trp Lys Ser Arg Leu Phe Arg His Ser Thr Gln Lys Asn Leu Lys	660	665	670	
15	Asn Ser Gln Met Cys Gln Lys Ser Leu Asp Val Glu Thr Asp Gly Leu	675	680	685	
	Glu Ala Asn Val Pro Pro Val Ser Phe Leu Lys Val Leu Lys Leu Asn	690	695	700	
20	Lys Thr Glu Trp Pro Tyr Phe Val Val Gly Thr Val Cys Ala Ile Ala	705	710	715	720
25	Asn Gly Gly Leu Gln Pro Ala Phe Ser Val Ile Phe Ser Glu Ile Ile	725	730	735	
	Ala Ile Phe Gly Pro Gly Asp Asp Ala Val Lys Gln Gln Lys Cys Asn	740	745	750	
30	Ile Phe Ser Leu Ile Phe Leu Phe Leu Gly Ile Ile Ser Phe Phe Thr	755	760	765	
35	Phe Phe Leu Gln Gly Phe Thr Phe Gly Lys Ala Gly Glu Ile Leu Thr	770	775	780	
40	Arg Arg Leu Arg Ser Met Ala Phe Lys Ala Met Leu Arg Gln Asp Met	785	790	795	800
	Ser Trp Phe Asp Asp His Lys Asn Ser Thr Gly Ala Leu Ser Thr Arg	805	810	815	
45	Leu Ala Thr Asp Ala Ala Gln Val Gln Gly Ala Thr Gly Thr Arg Leu	820	825	830	
50	Ala Leu Ile Ala Gln Asn Ile Ala Asn Leu Gly Thr Gly Ile Ile Ile	835	840	845	
	Ser Phe Ile Tyr Gly Trp Gln Leu Thr Leu Leu Leu Leu Ala Val Val	850	855	860	
55	Pro Ile Ile Ala Val Ser Gly Ile Val Glu Met Lys Leu Leu Ala Gly	865	870	875	880

EP 1 217 066 A1

5	Asn Ala Lys Arg Asp Lys Lys Glu Leu Glu Ala Ala Gly Lys Ile Ala	885	890	895
	Thr Glu Ala Ile Glu Asn Ile Arg Thr Val Val Ser Leu Thr Gln Glu	900	905	910
10	Arg Lys Phe Glu Ser Met Tyr Val Glu Lys Leu Tyr Gly Pro Tyr Arg	915	920	925
15	Val Phe Ser Ala Ile Val Phe Gly Ala Val Ala Leu Gly His Ala Ser	930	935	940
	Ser Phe Ala Pro Asp Tyr Ala Lys Ala Lys Leu Ser Ala Ala His Leu	945	950	955
20	Phe Met Leu Phe Glu Arg Gln Pro Leu Ile Asp Ser Tyr Ser Glu Glu	965	970	975
25	Gly Leu Lys Pro Asp Lys Phe Glu Gly Asn Ile Thr Phe Asn Glu Val	980	985	990
	Val Phe Asn Tyr Pro Thr Arg Ala Asn Val Pro Val Leu Gln Gly Leu	995	1000	1005
30	Ser Leu Glu Val Lys Lys Gly Gln Thr Leu Ala Leu Val Gly Ser Ser	1010	1015	1020
35	Gly Cys Gly Lys Ser Thr Val Val Gln Leu Leu Glu Arg Phe Tyr Asp	1025	1030	1035
	Pro Leu Ala Gly Thr Val Leu Leu Asp Gly Gln Glu Ala Lys Lys Leu	1045	1050	1055
40	Asn Val Gln Trp Leu Arg Ala Gln Leu Gly Ile Val Ser Gln Glu Pro	1060	1065	1070
45	Ile Leu Phe Asp Cys Ser Ile Ala Glu Asn Ile Ala Tyr Gly Asp Asn	1075	1080	1085
	Ser Arg Val Val Ser Gln Asp Glu Ile Val Ser Ala Ala Lys Ala Ala	1090	1095	1100
50	Asn Ile His Pro Phe Ile Glu Thr Leu Pro His Lys Tyr Glu Thr Arg	1105	1110	1115
	Val Gly Asp Lys Gly Thr Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile	1125	1130	1135

EP 1 217 066 A1

Ala Ile Ala Arg Ala Leu Ile Arg Gln Pro Gln Ile Leu Leu Leu Asp
5 1140 1145 1150

Glu Ala Thr Ser Ala Leu Asp Thr Glu Ser Glu Lys Val Val Gln Glu
1155 1160 1165

Ala Leu Asp Lys Ala Arg Glu Gly Arg Thr Cys Ile Val Ile Ala His
10 1170 1175 1180

Arg Leu Ser Thr Ile Gln Asn Ala Asp Leu Ile Val Val Phe Gln Asn
15 1185 1190 1195 1200

Gly Arg Val Lys Glu His Gly Thr His Gln Gln Leu Leu Ala Gln Lys
1205 1210 1215

Gly Ile Tyr Phe Ser Met Val Ser Val Gln Ala Gly Thr Gln Asn Leu
20 1220 1225 1230

25

30 <210> 54
<211> 842
<212> PRT
<213> Homo sapiens

35 <400> 54
Met Val Thr Val Gly Asn Tyr Cys Glu Ala Glu Gly Pro Val Gly Pro
1 5 10 15

40 Ala Trp Met Gln Asp Gly Leu Ser Pro Cys Phe Phe Phe Thr Leu Val
20 25 30

Pro Ser Thr Arg Met Ala Leu Gly Thr Leu Ala Leu Val Leu Ala Leu
45 35 40 45

Pro Cys Arg Arg Arg Glu Arg Pro Ala Gly Ala Asp Ser Leu Ser Trp
50 55 60

50 Gly Ala Gly Pro Arg Ile Ser Pro Tyr Val Leu Gln Leu Leu Leu Ala
65 70 75 80

Thr Leu Gln Ala Ala Leu Pro Leu Ala Gly Leu Ala Gly Arg Val Gly
55 85 90 95

EP 1 217 066 A1

	Thr	Ala	Arg	Gly	Ala	Pro	Leu	Pro	Ser	Tyr	Leu	Leu	Leu	Ala	Ser	Val	
				100					105					110			
5	Leu	Glu	Ser	Leu	Ala	Gly	Ala	Cys	Gly	Leu	Trp	Leu	Leu	Val	Val	Glu	
				115				120						125			
	Arg	Ser	Gln	Ala	Arg	Gln	Arg	Leu	Ala	Met	Gly	Ile	Trp	Ile	Lys	Phe	
10				130				135					140				
	Arg	His	Ser	Pro	Gly	Leu	Leu	Leu	Leu	Trp	Thr	Val	Ala	Phe	Ala	Ala	
	145					150					155					160	
15	Glu	Asn	Leu	Ala	Leu	Val	Ser	Trp	Asn	Ser	Pro	Gln	Trp	Trp	Trp	Ala	
					165					170						175	
	Arg	Ala	Asp	Leu	Gly	Gln	Gln	Val	Gln	Phe	Ser	Leu	Trp	Val	Leu	Arg	
20				180						185					190		
	Tyr	Val	Val	Ser	Gly	Gly	Leu	Phe	Val	Leu	Gly	Leu	Trp	Ala	Pro	Gly	
				195				200						205			
25	Leu	Arg	Pro	Gln	Ser	Tyr	Thr	Leu	Gln	Val	His	Glu	Glu	Asp	Gln	Asp	
		210					215						220				
	Val	Glu	Arg	Ser	Gln	Val	Arg	Ser	Ala	Ala	Gln	Gln	Ser	Thr	Trp	Arg	
30		225				230					235					240	
	Asp	Phe	Gly	Arg	Lys	Leu	Arg	Leu	Leu	Ser	Gly	Tyr	Leu	Trp	Pro	Arg	
35					245					250					255		
	Gly	Ser	Pro	Ala	Leu	Gln	Leu	Val	Val	Leu	Ile	Cys	Leu	Gly	Leu	Met	
				260					265						270		
40	Gly	Leu	Glu	Arg	Ala	Leu	Asn	Val	Leu	Val	Pro	Ile	Phe	Tyr	Arg	Asn	
			275					280					285				
	Ile	Val	Asn	Leu	Leu	Thr	Glu	Lys	Ala	Pro	Trp	Asn	Ser	Leu	Ala	Trp	
45			290				295					300					
	Thr	Val	Thr	Ser	Tyr	Val	Phe	Leu	Lys	Phe	Leu	Gln	Gly	Gly	Gly	Thr	
	305					310					315					320	
50	Gly	Ser	Thr	Gly	Phe	Val	Ser	Asn	Leu	Arg	Thr	Phe	Leu	Trp	Ile	Arg	
					325					330					335		
	Val	Gln	Gln	Phe	Thr	Ser	Arg	Arg	Val	Glu	Leu	Leu	Ile	Phe	Ser	His	
55					340				345					350			

EP 1 217 066 A1

	Leu His Glu Leu Ser Leu Arg Trp His Leu Gly Arg Arg Thr Gly Glu	
	355	360 365
5	Val Leu Arg Ile Ala Asp Arg Gly Thr Ser Ser Val Thr Gly Leu Leu	
	370	375 380
10	Ser Tyr Leu Val Phe Asn Val Ile Pro Thr Leu Ala Asp Ile Ile Ile	
	385	390 395 400
	Gly Ile Ile Tyr Phe Ser Met Phe Phe Asn Ala Trp Phe Gly Leu Ile	
		405 410 415
15	Val Phe Leu Cys Met Ser Leu Tyr Leu Thr Leu Thr Ile Val Val Thr	
		420 425 430
20	Glu Trp Arg Thr Lys Phe Arg Arg Ala Met Asn Thr Gln Glu Asn Ala	
		435 440 445
	Thr Arg Ala Arg Ala Val Asp Ser Leu Leu Asn Phe Glu Thr Val Lys	
		450 455 460
25	Tyr Tyr Asn Ala Glu Ser Tyr Glu Val Glu Arg Tyr Arg Glu Ala Ile	
		465 470 475 480
30	Ile Lys Tyr Gln Gly Leu Glu Trp Lys Ser Ser Ala Ser Leu Val Leu	
		485 490 495
	Leu Asn Gln Thr Gln Asn Leu Val Ile Gly Leu Gly Leu Leu Ala Gly	
		500 505 510
35	Ser Leu Leu Cys Ala Tyr Phe Val Thr Glu Gln Lys Leu Gln Val Gly	
		515 520 525
40	Asp Tyr Val Leu Phe Gly Thr Tyr Ile Ile Gln Leu Tyr Met Pro Leu	
		530 535 540
	Asn Trp Phe Gly Thr Tyr Tyr Arg Met Ile Gln Thr Asn Phe Ile Asp	
		545 550 555 560
45	Met Glu Asn Met Phe Asp Leu Leu Lys Glu Glu Thr Glu Val Lys Asp	
		565 570 575
50	Leu Pro Gly Ala Gly Pro Leu Arg Phe Gln Lys Gly Arg Ile Glu Phe	
		580 585 590
	Glu Asn Val His Phe Ser Tyr Ala Asp Gly Arg Glu Thr Leu Gln Asp	
		595 600 605
55		

EP 1 217 066 A1

Val Ser Phe Thr Val Met Pro Gly Gln Thr Leu Ala Leu Val Gly Pro
610 615 620

5 Ser Gly Ala Gly Lys Ser Thr Ile Leu Arg Leu Leu Phe Arg Phe Tyr
625 630 635 640

10 Asp Ile Ser Ser Gly Cys Ile Arg Ile Asp Gly Gln Asp Ile Ser Gln
645 650 655

Val Thr Gln Ala Ser Leu Arg Ser His Ile Gly Val Val Pro Gln Asp
660 665 670

15 Thr Val Leu Phe Asn Asp Thr Ile Ala Asp Asn Ile Arg Tyr Gly Arg
675 680 685

20 Val Thr Ala Gly Asn Asp Glu Val Glu Ala Ala Ala Gln Ala Ala Gly
690 695 700

Ile His Asp Ala Ile Met Ala Phe Pro Glu Gly Tyr Arg Thr Gln Val
705 710 715 720

25 Gly Glu Arg Gly Leu Lys Leu Ser Gly Gly Glu Lys Gln Arg Val Ala
725 730 735

30 Ile Ala Arg Thr Ile Leu Lys Ala Pro Gly Ile Ile Leu Leu Asp Glu
740 745 750

Ala Thr Ser Ala Leu Asp Thr Ser Asn Glu Arg Ala Ile Gln Ala Ser
755 760 765

35 Leu Ala Lys Val Cys Ala Asn Arg Thr Thr Ile Val Val Ala His Arg
770 775 780

40 Leu Ser Thr Val Val Asn Ala Asp Gln Ile Leu Val Ile Lys Asp Gly
785 790 795 800

Cys Ile Val Glu Arg Gly Arg His Glu Ala Leu Leu Ser Arg Gly Gly
805 810 815

45 Val Tyr Ala Asp Met Trp Gln Leu Gln Gln Gly Gln Glu Glu Thr Ser
820 825 830

50 Glu Asp Thr Lys Pro Gln Thr Met Glu Arg
835 840

55 <210> 55

EP 1 217 066 A1

<211> 752
<212> PRT
<213> Homo sapiens

<400> 55

Met	Ala	Leu	Leu	Ala	Met	His	Ser	Trp	Arg	Trp	Ala	Ala	Ala	Ala	Ala
1				5					10				15		
Ala	Phe	Glu	Lys	Arg	Arg	His	Ser	Ala	Ile	Leu	Ile	Arg	Pro	Leu	Val
			20					25					30		
Ser	Val	Ser	Gly	Ser	Gly	Pro	Gln	Trp	Arg	Pro	His	Gln	Leu	Gly	Ala
		35					40					45			
Leu	Gly	Thr	Ala	Arg	Ala	Tyr	Gln	Ile	Pro	Glu	Ser	Leu	Lys	Ser	Ile
	50					55				60					
Thr	Trp	Gln	Arg	Leu	Gly	Lys	Gly	Asn	Ser	Gly	Gln	Phe	Leu	Asp	Ala
65				70					75					80	
Ala	Lys	Ala	Leu	Gln	Val	Trp	Pro	Leu	Ile	Glu	Lys	Arg	Thr	Cys	Trp
			85					90						95	
His	Gly	His	Ala	Gly	Gly	Gly	Leu	His	Thr	Asp	Pro	Lys	Glu	Gly	Leu
			100				105						110		
Lys	Asp	Val	Asp	Thr	Arg	Lys	Ile	Ile	Lys	Ala	Met	Leu	Ser	Tyr	Val
	115						120					125			
Trp	Pro	Lys	Asp	Arg	Pro	Asp	Leu	Arg	Ala	Arg	Val	Pro	Ile	Ser	Leu
	130					135					140				
Gly	Phe	Leu	Gly	Gly	Ala	Lys	Ala	Met	Asn	Ile	Val	Val	Pro	Phe	Met
145					150				155					160	
Phe	Lys	Tyr	Ala	Val	Asp	Ser	Leu	Asn	Gln	Met	Ser	Gly	Asn	Met	Leu
			165					170					175		
Asn	Leu	Ser	Asp	Ala	Pro	Asn	Thr	Val	Ala	Thr	Met	Ala	Thr	Ala	Val
			180				185						190		
Leu	Ile	Gly	Tyr	Gly	Val	Ser	Arg	Ala	Gly	Ala	Ala	Phe	Phe	Asn	Glu
	195					200						205			
Val	Arg	Asn	Ala	Val	Phe	Gly	Lys	Val	Ala	Gln	Asn	Ser	Ile	Arg	Arg
	210				215					220					
Ile	Ala	Lys	Asn	Val	Phe	Leu	His	Leu	His	Asn	Leu	Asp	Leu	Gly	Phe

EP 1 217 066 A1

	225		230		235		240									
5	His	Leu	Ser	Arg	Gln	Thr	Gly	Ala	Leu	Ser	Lys	Ala	Ile	Asp	Arg	Gly
					245					250					255	
	Thr	Arg	Gly	Ile	Ser	Phe	Val	Leu	Ser	Ala	Leu	Val	Phe	Asn	Pro	Leu
10				260					265					270		
	Pro	Asn	His	Val	Glu	Val	Met	Leu	Leu	Val	Ser	Gly	Val	Leu	Tyr	Tyr
			275					280					285			
15	Lys	Cys	Cys	Ala	Gln	Leu	Leu	Gly	Asn	Leu	Gly	Thr	Leu	Gly	Thr	Tyr
		290				295				300						
	Thr	Ala	Phe	Thr	Val	Ala	Val	Thr	Arg	Trp	Arg	Thr	Arg	Phe	Arg	Leu
20	305					310				315						320
	Glu	Ile	Asp	Gln	Ala	Asp	Asn	Asp	Ala	Gly	Asn	Ala	Ala	Ile	Asp	Ser
				325					330					335		
25	Leu	Leu	Asn	Tyr	Glu	Thr	Val	Lys	Tyr	Phe	Asn	Asn	Glu	Arg	Tyr	Glu
				340				345					350			
	Ala	Gln	Arg	Tyr	Asp	Gly	Phe	Leu	Lys	Thr	Tyr	Glu	Thr	Ala	Ser	Leu
30			355					360				365				
	Lys	Ser	Thr	Ser	Thr	Leu	Ala	Met	Leu	Asn	Phe	Gly	Gln	Ser	Ala	Ile
		370				375				380						
35	Phe	Ser	Val	Gly	Leu	Thr	Ala	Ile	Met	Val	Leu	Ala	Ser	Gln	Gly	Ile
	385				390				395				400			
	Val	Ala	Gly	Thr	Leu	Thr	Val	Gly	Asp	Leu	Val	Met	Val	Asn	Gly	Leu
40				405				410				415				
	Leu	Phe	Gln	Leu	Ser	Leu	Pro	Leu	Asn	Phe	Leu	Gly	Thr	Val	Tyr	Arg
			420				425				430					
45	Glu	Thr	Arg	Gln	Ala	Leu	Ile	Asp	Met	Asn	Thr	Leu	Phe	Thr	Leu	Leu
		435				440				445						
	Lys	Val	Asp	Thr	Gln	Ile	Lys	Asp	Lys	Val	Met	Ala	Ser	Pro	Leu	Gln
50		450				455				460						
	Ile	Thr	Pro	Gln	Thr	Ala	Thr	Val	Ala	Phe	Asp	Asn	Val	His	Phe	Glu
	465				470				475				480			
55	Tyr	Ile	Glu	Gly	Gln	Lys	Val	Leu	Ser	Gly	Ile	Ser	Phe	Glu	Val	Pro

EP 1 217 066 A1

	485	490	495
5	Ala Gly Lys Lys Val	Ala Ile Val Gly Gly Ser Gly Ser Gly Lys Ser	
	500	505	510
10	Thr Ile Val Arg Leu Leu Phe Arg Phe Tyr Glu Pro Gln Lys Gly Ser		
	515	520	525
15	Ile Tyr Leu Ala Gly Gln Asn Ile Gln Asp Val Ser Leu Glu Ser Leu		
	530	535	540
20	Arg Arg Ala Val Gly Val Val Pro Gln Asp Ala Val Leu Phe His Asn		
	545	550	555
25	Thr Ile Tyr Tyr Asn Leu Leu Tyr Gly Asn Ile Ser Ala Ser Pro Glu		
	565	570	575
30	Glu Val Tyr Ala Val Ala Lys Leu Ala Gly Leu His Asp Ala Ile Leu		
	580	585	590
35	Arg Met Pro His Gly Tyr Asp Thr Gln Val Gly Glu Arg Gly Leu Lys		
	595	600	605
40	Leu Ser Gly Gly Glu Lys Gln Arg Val Ala Ile Ala Arg Ala Ile Leu		
	610	615	620
45	Lys Asp Pro Pro Val Ile Leu Tyr Asp Glu Ala Thr Ser Ser Leu Asp		
	625	630	635
50	Ser Ile Thr Glu Glu Thr Ile Leu Gly Ala Met Lys Asp Val Val Lys		
	645	650	655
55	His Arg Thr Ser Ile Phe Ile Ala His Arg Leu Ser Thr Val Val Asp		
	660	665	670
60	Ala Asp Glu Ile Ile Val Leu Asp Gln Gly Lys Val Ala Glu Arg Gly		
	675	680	685
65	Thr His His Gly Leu Leu Ala Asn Pro His Ser Ile Tyr Ser Glu Met		
	690	695	700
70	Trp His Thr Gln Ser Ser Arg Val Gln Asn His Asp Asn Pro Lys Trp		
	705	710	715
75	Glu Ala Lys Lys Glu Asn Ile Ser Lys Glu Glu Glu Arg Lys Lys Leu		
	725	730	735
80	Gln Glu Glu Ile Val Asn Ser Val Lys Gly Cys Gly Asn Cys Ser Cys		

EP 1 217 066 A1

	740	745	750
5			
10	<210> 56 <211> 718 <212> PRT <213> Homo sapiens		
15	<400> 56 Met Leu Val His Leu Phe Arg Val Gly Ile Arg Gly Gly Pro Phe Pro 1 5 10 15		
20	Gly Arg Leu Leu Pro Pro Leu Arg Phe Gln Thr Phe Ser Ala Val Arg 20 25 30		
25	Tyr Ser Asp Gly Tyr Arg Ser Ser Ser Leu Leu Arg Ala Val Ala His 35 40 45		
30	Leu Arg Ser Gln Leu Trp Ala His Leu Pro Arg Ala Pro Leu Ala Pro 50 55 60		
35	Arg Trp Ser Pro Ser Ala Trp Cys Trp Val Gly Gly Ala Leu Leu Gly 65 70 75 80		
40	Pro Met Val Leu Ser Lys His Pro His Leu Cys Leu Val Ala Leu Cys 85 90 95		
45	Glu Ala Glu Glu Ala Pro Pro Ala Ser Ser Thr Pro His Val Val Gly 100 105 110		
50	Ser Arg Phe Asn Trp Lys Leu Phe Trp Gln Phe Leu His Pro His Leu 115 120 125		
55	Leu Val Leu Gly Val Ala Val Val Leu Ala Leu Gly Ala Ala Leu Val 130 135 140		
	Asn Val Gln Ile Pro Leu Leu Leu Gly Gln Leu Val Lys Val Val Ala 145 150 155 160		
	Lys Tyr Thr Arg Asp His Val Gly Ser Phe Met Thr Glu Ser Gln Asn 165 170 175		
	Leu Ser Thr His Leu Leu Ile Leu Tyr Gly Val Gln Gly Leu Leu Thr 180 185 190		

EP 1 217 066 A1

5	Phe Gly Tyr Leu Val Leu Leu Ser His Val Gly Glu Arg Met Ala Val	195	200	205
10	Asp Met Arg Arg Ala Leu Phe Ser Ser Leu Leu Arg Gln Asn Ile Thr	210	215	220
15	Phe Phe Asp Ala Asn Lys Thr Gly Gln Leu Val Ser Arg Leu Thr Thr	225	230	235
				240
	Asp Val Gln Glu Phe Lys Ser Ser Phe Lys Leu Val Ile Ser Gln Gly	245	250	255
	Leu Arg Ser Cys Ser Gln Val Ala Gly Cys Leu Val Ser Leu Ser Met	260	265	270
20	Leu Ser Thr Arg Leu Thr Leu Leu Leu Met Val Ala Thr Pro Ala Leu	275	280	285
25	Met Gly Val Gly Thr Leu Met Gly Ser Gly Leu Arg Lys Leu Ser Arg	290	295	300
	Gln Cys Gln Glu His Ile Ala Arg Ala Met Gly Val Ala Asp Glu Ala	305	310	315
				320
30	Leu Gly Asn Val Arg Thr Val Arg Ala Leu Ala Met Glu Gln Arg Glu	325	330	335
35	Glu Glu Arg Tyr Gly Ala Glu Leu Glu Ala Cys Arg Cys Arg Ala Glu	340	345	350
	Glu Leu Gly Arg Gly Ile Ala Leu Phe Gln Gly Leu Ser Asn Ile Ala	355	360	365
40	Phe Asn Cys Met Val Leu Gly Thr Leu Phe Ile Gly Gly Ser Leu Val	370	375	380
45	Ala Gly Gln Gln Leu Thr Gly Gly Asp Leu Met Ser Phe Leu Val Ala	385	390	395
				400
	Ser Gln Thr Val Gln Arg Ser Met Ala Asn Leu Ser Val Leu Phe Gly	405	410	415
50	Gln Val Val Arg Gly Leu Ser Ala Gly Ala Arg Val Phe Glu Tyr Met	420	425	430
55	Ala Leu Asn Pro Cys Ile Pro Leu Ser Gly Gly Cys Cys Val Pro Lys	435	440	445

EP 1 217 066 A1

	Glu Gln Leu Arg Gly Ser Val Thr Phe Gln Asn Val Cys Phe Ser Tyr	
	450	455 460
5		
	Pro Cys Arg Pro Gly Phe Glu Val Leu Lys Asp Phe Thr Leu Thr Leu	
	465	470 475 480
10		
	Pro Pro Gly Lys Ile Val Ala Leu Val Gly Gln Ser Gly Gly Gly Lys	
		485 490 495
	Thr Thr Val Ala Ser Leu Leu Glu Arg Phe Tyr Asp Pro Thr Ala Gly	
15		500 505 510
	Val Val Met Leu Asp Gly Arg Asp Leu Arg Thr Leu Asp Pro Ser Trp	
		515 520 525
20		
	Leu Arg Gly Gln Val Val Gly Phe Ile Ser Gln Glu Pro Val Leu Phe	
		530 535 540
	Gly Thr Thr Ile Met Glu Asn Ile Arg Phe Gly Lys Leu Glu Ala Ser	
25		545 550 555 560
	Asp Glu Glu Val Tyr Thr Ala Ala Arg Glu Ala Asn Ala His Glu Phe	
		565 570 575
30		
	Ile Thr Ser Phe Pro Glu Gly Tyr Asn Thr Val Val Gly Glu Arg Gly	
		580 585 590
	Thr Thr Leu Ser Gly Gly Gln Lys Gln Arg Leu Ala Ile Ala Arg Ala	
35		595 600 605
	Leu Ile Lys Gln Pro Thr Val Leu Ile Leu Asp Glu Ala Thr Ser Ala	
		610 615 620
40		
	Leu Asp Ala Glu Ser Glu Arg Val Val Gln Glu Ala Leu Asp Arg Ala	
		625 630 635 640
	Ser Ala Gly Arg Thr Val Leu Val Ile Ala His Arg Leu Ser Thr Val	
45		645 650 655
	Arg Gly Ala His Cys Ile Val Val Met Ala Asp Gly Arg Val Trp Glu	
		660 665 670
50		
	Ala Gly Thr His Glu Glu Leu Leu Lys Lys Gly Gly Leu Tyr Ala Glu	
		675 680 685
	Leu Ile Arg Arg Gln Ala Leu Asp Ala Pro Arg Thr Ala Ala Pro Pro	
55		690 695 700

EP 1 217 066 A1

Pro Lys Lys Pro Glu Gly Pro Arg Ser His Gln His Lys Ser
705 710 715

5

<210> 57
10 <211> 723
<212> PRT
<213> Homo sapiens

15 <400> 57
Met Arg Leu Trp Lys Ala Val Val Val Thr Leu Ala Phe Met Ser Val
1 5 10 15

20 Asp Ile Cys Val Thr Thr Ala Ile Tyr Val Phe Ser His Leu Asp Arg
20 25 30

Ser Leu Leu Glu Asp Ile Arg His Phe Asn Ile Phe Asp Ser Val Leu
35 40 45

25 Asp Leu Trp Ala Ala Cys Leu Tyr Arg Ser Cys Leu Leu Leu Gly Ala
50 55 60

30 Thr Ile Gly Val Ala Lys Asn Ser Ala Leu Gly Pro Arg Arg Leu Arg
65 70 75 80

Ala Ser Trp Leu Val Ile Thr Leu Val Cys Leu Phe Val Gly Ile Tyr
85 90 95

35 Ala Met Val Lys Leu Leu Leu Phe Ser Glu Val Arg Arg Pro Ile Arg
100 105 110

40 Asp Pro Trp Phe Trp Ala Leu Phe Val Trp Thr Tyr Ile Ser Leu Gly
115 120 125

Ala Ser Phe Leu Leu Trp Trp Leu Leu Ser Thr Val Arg Pro Gly Thr
130 135 140

45 Gln Ala Leu Glu Pro Gly Ala Ala Thr Glu Ala Glu Gly Phe Pro Gly
145 150 155 160

50 Ser Gly Arg Pro Pro Pro Glu Gln Ala Ser Gly Ala Thr Leu Gln Lys
165 170 175

Leu Leu Ser Tyr Thr Lys Pro Asp Val Ala Phe Leu Val Ala Ala Ser
180 185 190

55

EP 1 217 066 A1

	Phe Phe Leu Ile Val Ala Ala Leu Gly Glu Thr Phe Leu Pro Tyr Tyr	
	195	200 205
5	Thr Gly Arg Ala Ile Asp Gly Ile Val Ile Gln Lys Ser Met Asp Gln	
	210	215 220
	Phe Ser Thr Ala Val Val Ile Val Cys Leu Leu Ala Ile Gly Ser Ser	
10	225	230 235 240
	Phe Ala Ala Gly Ile Arg Gly Gly Ile Phe Thr Leu Ile Phe Ala Arg	
		245 250 255
15	Leu Asn Ile Arg Leu Arg Asn Cys Leu Phe Arg Ser Leu Val Ser Gln	
		260 265 270
	Glu Thr Ser Phe Phe Asp Glu Asn Arg Thr Gly Asp Leu Ile Ser Arg	
20		275 280 285
	Leu Thr Ser Asp Thr Thr Met Val Ser Asp Leu Val Ser Gln Asn Ile	
	290	295 300
25	Asn Val Phe Leu Arg Asn Thr Val Lys Val Thr Gly Val Val Val Phe	
	305	310 315 320
	Met Phe Ser Leu Ser Trp Gln Leu Ser Leu Val Thr Phe Met Gly Phe	
30		325 330 335
	Pro Ile Ile Met Met Val Ser Asn Ile Tyr Gly Lys Tyr Tyr Lys Arg	
		340 345 350
35	Leu Ser Lys Glu Val Gln Asn Ala Leu Ala Arg Ala Ser Asn Thr Ala	
	355	360 365
	Glu Glu Thr Ile Ser Ala Met Lys Thr Val Arg Ser Phe Ala Asn Glu	
40		370 375 380
	Glu Glu Glu Ala Glu Val Tyr Leu Arg Lys Leu Gln Gln Val Tyr Lys	
45	385	390 395 400
	Leu Asn Arg Lys Glu Ala Ala Ala Tyr Met Tyr Tyr Val Trp Gly Ser	
		405 410 415
50	Gly Ser Val Gly Ser Val Tyr Ser Gly Leu Met Gln Gly Val Gly Ala	
		420 425 430
	Ala Glu Lys Val Phe Glu Phe Ile Asp Arg Gln Pro Thr Met Val His	
55		435 440 445

EP 1 217 066 A1

	Asp Gly Ser Leu Ala Pro Asp His Leu Glu Gly Arg Val Asp Phe Glu	
	450	455 460
5	Asn Val Thr Phe Thr Tyr Arg Thr Arg Pro His Thr Gln Val Leu Gln	
	465	470 475 480
	Asn Val Ser Phe Ser Leu Ser Pro Gly Lys Val Thr Ala Leu Val Gly	
10		485 490 495
	Pro Ser Gly Ser Gly Lys Ser Ser Cys Val Asn Ile Leu Glu Asn Phe	
	500	505 510
15	Tyr Pro Leu Glu Gly Gly Arg Val Leu Leu Asp Gly Lys Pro Ile Ser	
	515	520 525
	Ala Tyr Asp His Lys Tyr Leu His Arg Val Ile Ser Leu Val Ser Gln	
20		530 535 540
	Glu Pro Val Leu Phe Ala Arg Ser Ile Thr Asp Asn Ile Ser Tyr Gly	
	545	550 555 560
25	Leu Pro Thr Val Pro Phe Glu Met Val Val Glu Ala Ala Gln Lys Ala	
		565 570 575
	Asn Ala His Gly Phe Ile Met Glu Leu Gln Asp Gly Tyr Ser Thr Glu	
30		580 585 590
	Thr Gly Glu Lys Gly Ala Gln Leu Ser Gly Gly Gln Lys Gln Arg Val	
	595	600 605
35	Ala Met Ala Arg Ala Leu Val Arg Asn Pro Pro Val Leu Ile Leu Asp	
	610	615 620
	Glu Ala Thr Ser Ala Leu Asp Ala Glu Ser Glu Tyr Leu Ile Gln Gln	
40		625 630 635 640
	Ala Ile His Gly Asn Leu Gln Lys His Thr Val Leu Ile Ile Ala His	
		645 650 655
45	Arg Leu Ser Thr Val Glu His Ala His Leu Ile Val Val Leu Asp Lys	
	660	665 670
	Gly Arg Val Val Gln Gln Gly Thr His Gln Gln Leu Leu Ala Gln Gly	
50		675 680 685
	Gly Leu Tyr Ala Lys Leu Val Gln Arg Gln Met Leu Gly Leu Gln Pro	
55		690 695 700

EP 1 217 066 A1

Ala Ala Asp Phe Thr Ala Gly His Asn Glu Pro Val Ala Asn Gly Ser
705 710 715 720

5 His Lys Ala

10 <210> 58
<211> 738
<212> PRT
15 <213> Homo sapiens

<400> 58
Met Arg Gly Pro Pro Ala Trp Pro Leu Arg Leu Leu Glu Pro Pro Ser
1 5 10 15

20 Pro Ala Glu Pro Gly Arg Leu Leu Pro Val Ala Cys Val Trp Ala Ala
20 25 30

25 Ala Ser Arg Val Pro Gly Ser Leu Ser Pro Phe Thr Gly Leu Arg Pro
35 40 45

30 Ala Arg Leu Trp Gly Ala Gly Pro Ala Leu Leu Trp Gly Val Gly Ala
50 55 60

Ala Arg Arg Trp Arg Ser Gly Cys Arg Gly Gly Gly Pro Gly Ala Ser
65 70 75 80

35 Arg Gly Val Leu Gly Leu Ala Arg Leu Leu Gly Leu Trp Ala Arg Gly
85 90 95

40 Pro Gly Ser Cys Arg Cys Gly Ala Phe Ala Gly Pro Gly Ala Pro Arg
100 105 110

Leu Pro Arg Ala Arg Phe Pro Gly Gly Pro Ala Ala Ala Ala Trp Ala
115 120 125

45 Gly Asp Glu Ala Trp Arg Arg Gly Pro Ala Ala Pro Pro Gly Asp Lys
130 135 140

50 Gly Arg Leu Arg Pro Ala Ala Ala Gly Leu Pro Glu Ala Arg Lys Leu
145 150 155 160

Leu Gly Leu Ala Tyr Pro Glu Arg Arg Arg Leu Ala Ala Ala Val Gly
165 170 175

55 Phe Leu Thr Met Ser Ser Val Ile Ser Met Ser Ala Pro Phe Phe Leu

EP 1 217 066 A1

	180	185	190
5	Gly Lys Ile Ile Asp Val Ile Tyr Thr Asn Pro Thr Val Asp Tyr Ser 195	200	205
10	Asp Asn Leu Thr Arg Leu Cys Leu Gly Leu Ser Ala Val Phe Leu Cys 210	215	220
	Gly Ala Ala Ala Asn Ala Ile Arg Val Tyr Leu Met Gln Thr Ser Gly 225	230	235 240
15	Gln Arg Ile Val Asn Arg Leu Arg Thr Ser Leu Phe Ser Ser Ile Leu 245	250	255
20	Arg Gln Glu Val Ala Phe Phe Asp Lys Thr Arg Thr Gly Glu Leu Ile 260	265	270
	Asn Arg Leu Ser Ser Asp Thr Ala Leu Leu Gly Arg Ser Val Thr Glu 275	280	285
25	Asn Leu Ser Asp Gly Leu Arg Ala Gly Ala Gln Ala Ser Val Gly Ile 290	295	300
30	Ser Met Met Phe Phe Val Ser Pro Asn Leu Ala Thr Phe Val Leu Ser 305	310	315 320
	Val Val Pro Pro Val Ser Ile Ile Ala Val Ile Tyr Gly Arg Tyr Leu 325	330	335
35	Arg Lys Leu Thr Lys Val Thr Gln Asp Ser Leu Ala Gln Ala Thr Gln 340	345	350
40	Leu Ala Glu Glu Arg Ile Gly Asn Val Arg Thr Val Arg Ala Phe Gly 355	360	365
	Lys Glu Met Thr Glu Ile Glu Lys Tyr Ala Ser Lys Val Asp His Val 370	375	380
45	Met Gln Leu Ala Arg Lys Glu Ala Val Ala Arg Ala Gly Phe Phe Gly 385	390	395 400
50	Ala Thr Gly Leu Ser Gly Asn Leu Ile Val Leu Ser Val Leu Tyr Lys 405	410	415
	Gly Gly Leu Leu Met Gly Ser Ala His Met Thr Val Gly Glu Leu Ser 420	425	430
55	Ser Phe Leu Met Tyr Ala Phe Trp Val Gly Ile Ser Ile Gly Gly Leu		

EP 1 217 066 A1

	435		440		445	
5	Ser Ser Phe Tyr Ser Glu Leu Met Lys Gly Leu Gly Ala Gly Gly Arg					
	450		455		460	
	Leu Trp Glu Leu Leu Glu Arg Glu Pro Lys Leu Pro Phe Asn Glu Gly					
	465		470		475	480
10	Val Ile Leu Asn Glu Lys Ser Phe Gln Gly Ala Leu Glu Phe Lys Asn					
		485		490		495
15	Val His Phe Ala Tyr Pro Ala Arg Pro Glu Val Pro Ile Phe Gln Asp					
		500		505		510
	Phe Ser Leu Ser Ile Pro Ser Gly Ser Val Thr Ala Leu Val Gly Pro					
20		515		520		525
	Ser Gly Ser Gly Lys Ser Thr Val Leu Ser Leu Leu Leu Arg Leu Tyr					
		530		535		540
25	Asn Pro Ala Ser Gly Thr Ile Ser Leu Asp Gly His Asp Ile Arg Gln					
		545		550		555
	Leu Asn Pro Val Trp Leu Arg Ser Lys Ile Gly Thr Val Ser Gln Glu					
30			565		570	575
	Pro Ile Leu Phe Ser Cys Ser Ile Ala Glu Asn Ile Ala Tyr Gly Ala					
		580		585		590
35	Asp Asp Pro Ser Ser Val Thr Ala Glu Glu Ile Gln Arg Val Ala Glu					
		595		600		605
	Val Ala Asn Ala Val Ala Phe Ile Arg Asn Phe Pro Gln Gly Phe Asn					
40		610		615		620
	Thr Val Val Gly Glu Lys Gly Val Leu Leu Ser Gly Gly Gln Lys Gln					
		625		630		635
						640
45	Arg Ile Ala Ile Ala Arg Ala Leu Leu Lys Asn Pro Lys Ile Leu Leu					
		645		650		655
	Leu Asp Glu Ala Thr Ser Ala Leu Asp Ala Glu Asn Glu Tyr Leu Val					
50		660		665		670
	Gln Glu Ala Leu Asp Arg Leu Met Asp Gly Arg Thr Val Leu Val Ile					
		675		680		685
55	Ala His Arg Leu Ser Thr Ile Lys Asn Ala Asn Met Val Ala Val Leu					

690 695 700

112

EP 1 217 066 A1

	Cys Phe Trp Val Ile Ala Ala Ala Arg Gln Ile Gln Lys Met Arg Lys	
	165	170 175
5	Phe Tyr Phe Arg Arg Ile Met Arg Met Glu Ile Gly Trp Phe Asp Cys	
	180	185 190
10	Asn Ser Val Gly Glu Leu Asn Thr Arg Phe Ser Asp Asp Ile Asn Lys	
	195	200 205
	Ile Asn Asp Ala Ile Ala Asp Gln Met Ala Leu Phe Ile Gln Arg Met	
15	210	215 220
	Thr Ser Thr Ile Cys Gly Phe Leu Leu Gly Phe Phe Arg Gly Trp Lys	
	225	230 235 240
20	Leu Thr Leu Val Ile Ile Ser Val Ser Pro Leu Ile Gly Ile Gly Ala	
	245	250 255
	Ala Thr Ile Gly Leu Ser Val Ser Lys Phe Thr Asp Tyr Glu Leu Lys	
25	260	265 270
	Ala Tyr Ala Lys Ala Gly Val Val Ala Asp Glu Val Ile Ser Ser Met	
	275	280 285
30	Arg Thr Val Ala Ala Phe Gly Gly Glu Lys Arg Glu Val Glu Arg Tyr	
	290	295 300
	Glu Lys Asn Leu Val Phe Ala Gln Arg Trp Gly Ile Arg Lys Gly Ile	
35	305	310 315 320
	Val Met Gly Phe Phe Thr Gly Phe Val Trp Cys Leu Ile Phe Leu Cys	
	325	330 335
40	Tyr Ala Val Ala Phe Trp Tyr Gly Ser Thr Leu Val Leu Asp Glu Gly	
	340	345 350
	Glu Tyr Thr Pro Gly Thr Leu Val Gln Ile Phe Leu Ser Val Ile Val	
45	355	360 365
	Gly Ala Leu Asn Leu Gly Asn Ala Ser Pro Cys Leu Glu Ala Phe Ala	
	370	375 380
50	Thr Gly Arg Ala Ala Ala Thr Ser Ile Phe Glu Thr Ile Asp Arg Lys	
	385	390 395 400
55	Pro Ile Ile Asp Cys Met Ser Glu Asp Gly Tyr Lys Leu Asp Arg Ile	
	405	410 415

EP 1 217 066 A1

	Lys Gly Glu Ile Glu Phe His Asn Val Thr Phe His Tyr Pro Ser Arg	
	420	425 430
5	Pro Glu Val Lys Ile Leu Asn Asp Leu Asn Met Val Ile Lys Pro Gly	
	435	440 445
10	Glu Met Thr Ala Leu Val Gly Pro Ser Gly Ala Gly Lys Ser Thr Ala	
	450	455 460
	Leu Gln Leu Ile Gln Arg Phe Tyr Asp Pro Cys Glu Gly Met Val Thr	
15	465	470 475 480
	Val Asp Gly His Asp Ile Arg Ser Leu Asn Ile Gln Trp Leu Arg Asp	
	485	490 495
20	Gln Ile Gly Ile Val Glu Gln Glu Pro Val Leu Phe Ser Thr Thr Ile	
	500	505 510
	Ala Glu Asn Ile Arg Tyr Gly Arg Glu Asp Ala Thr Met Glu Asp Ile	
25	515	520 525
	Val Gln Ala Ala Lys Glu Ala Asn Ala Tyr Asn Phe Ile Met Asp Leu	
	530	535 540
30	Pro Gln Gln Phe Asp Thr Leu Val Gly Glu Gly Gly Gly Gln Met Ser	
	545	550 555 560
	Gly Gly Gln Lys Gln Arg Val Ala Ile Ala Arg Ala Leu Ile Arg Asn	
35	565	570 575
	Pro Lys Ile Leu Leu Leu Asp Met Ala Thr Ser Ala Leu Asp Asn Glu	
	580	585 590
40	Ser Glu Ala Met Val Gln Glu Val Leu Ser Lys Ile Gln His Gly His	
	595	600 605
	Thr Ile Ile Ser Val Ala His Arg Leu Ser Thr Val Arg Ala Ala Asp	
45	610	615 620
	Thr Ile Ile Gly Phe Glu His Gly Thr Ala Val Glu Arg Gly Thr His	
	625	630 635 640
50	Glu Glu Leu Leu Glu Arg Lys Gly Val Tyr Phe Thr Leu Val Thr Leu	
	645	650 655
	Gln Ser Gln Gly Asn Gln Ala Leu Asn Glu Glu Asp Ile Lys Asp Ala	
55	660	665 670

EP 1 217 066 A1

	Thr	Glu	Asp	Asp	Met	Leu	Ala	Arg	Thr	Phe	Ser	Arg	Gly	Ser	Tyr	Gln	
5																	
	Asp	Ser	Leu	Arg	Ala	Ser	Ile	Arg	Gln	Arg	Ser	Lys	Ser	Gln	Leu	Ser	
10																	
	Tyr	Leu	Val	His	Glu	Pro	Pro	Leu	Ala	Val	Val	Asp	His	Lys	Ser	Thr	
15																	
	Tyr	Glu	Glu	Asp	Arg	Lys	Asp	Lys	Asp	Ile	Pro	Val	Gln	Glu	Glu	Val	
	Glu	Pro	Ala	Pro	Val	Arg	Arg	Ile	Leu	Lys	Phe	Ser	Ala	Pro	Glu	Trp	
20																	
	Pro	Tyr	Met	Leu	Val	Gly	Ser	Val	Gly	Ala	Ala	Val	Asn	Gly	Thr	Val	
25																	
	Thr	Pro	Leu	Tyr	Ala	Phe	Leu	Phe	Ser	Gln	Ile	Leu	Gly	Thr	Phe	Ser	
	Ile	Pro	Asp	Lys	Glu	Glu	Gln	Arg	Ser	Gln	Ile	Asn	Gly	Val	Cys	Leu	
30																	
	Leu	Phe	Val	Ala	Met	Gly	Cys	Val	Ser	Leu	Phe	Thr	Gln	Phe	Leu	Gln	
35																	
	Gly	Tyr	Ala	Phe	Ala	Lys	Ser	Gly	Glu	Leu	Leu	Thr	Lys	Arg	Leu	Arg	
	Lys	Phe	Gly	Phe	Arg	Ala	Met	Leu	Gly	Gln	Asp	Ile	Ala	Trp	Phe	Asp	
40																	
	Asp	Leu	Arg	Asn	Ser	Pro	Gly	Ala	Leu	Thr	Thr	Arg	Leu	Ala	Thr	Asp	
45																	
	Ala	Ser	Gln	Val	Gln	Gly	Ala	Ala	Gly	Ser	Gln	Ile	Gly	Met	Ile	Val	
	Asn	Ser	Phe	Thr	Asn	Val	Thr	Val	Ala	Met	Ile	Ile	Ala	Phe	Ser	Phe	
50																	
	Ser	Trp	Lys	Leu	Ser	Leu	Val	Ile	Leu	Cys	Phe	Phe	Pro	Phe	Leu	Ala	
55																	
	Leu	Ser	Gly	Ala	Thr	Gln	Thr	Arg	Met	Leu	Thr	Gly	Phe	Ala	Ser	Arg	

EP 1 217 066 A1

5	Asp Lys Gln Ala Leu Glu Met Val Gly Gln Ile Thr Asn Glu Ala Leu	930	935	940
	Ser Asn Ile Arg Thr Val Ala Gly Ile Gly Lys Glu Arg Arg Phe Ile	945	950	955 960
10	Glu Ala Leu Glu Thr Glu Leu Glu Lys Pro Phe Lys Thr Ala Ile Gln	965	970	975
15	Lys Ala Asn Ile Tyr Gly Phe Cys Phe Ala Phe Ala Gln Cys Ile Met	980	985	990
	Phe Ile Ala Asn Ser Ala Ser Tyr Arg Tyr Gly Gly Tyr Leu Ile Ser	995	1000	1005
20	Asn Glu Gly Leu His Phe Ser Tyr Val Phe Arg Val Ile Ser Ala Val	1010	1015	1020
25	Val Leu Ser Ala Thr Ala Leu Gly Arg Ala Phe Ser Tyr Thr Pro Ser	1025	1030	1035 1040
	Tyr Ala Lys Ala Lys Ile Ser Ala Ala Arg Phe Phe Gln Leu Leu Asp	1045	1050	1055
30	Arg Gln Pro Pro Ile Ser Val Tyr Asn Thr Ala Gly Glu Lys Trp Asp	1060	1065	1070
35	Asn Phe Gln Gly Lys Ile Asp Phe Val Asp Cys Lys Phe Thr Tyr Pro	1075	1080	1085
	Ser Arg Pro Asp Ser Gln Val Leu Asn Gly Leu Ser Val Ser Ile Ser	1090	1095	1100
40	Pro Gly Gln Thr Leu Ala Phe Val Gly Ser Ser Gly Cys Gly Lys Ser	1105	1110	1115 1120
45	Thr Ser Ile Gln Leu Leu Glu Arg Phe Tyr Asp Pro Asp Gln Gly Lys	1125	1130	1135
	Val Met Ile Asp Gly His Asp Ser Lys Lys Val Asn Val Gln Phe Leu	1140	1145	1150
50	Arg Ser Asn Ile Gly Ile Val Ser Gln Glu Pro Val Leu Phe Ala Cys	1155	1160	1165
55	Ser Ile Met Asp Asn Ile Lys Tyr Gly Asp Asn Thr Lys Glu Ile Pro	1170	1175	1180

EP 1 217 066 A1

5 Met Glu Arg Val Ile Ala Ala Ala Lys Gln Ala Gln Leu His Asp Phe
 1185 1190 1195 1200
 Val Met Ser Leu Pro Glu Lys Tyr Glu Thr Asn Val Gly Ser Gln Gly
 1205 1210 1215
 10 Ser Gln Leu Ser Arg Gly Glu Lys Gln Arg Ile Ala Ile Ala Arg Ala
 1220 1225 1230
 Ile Val Arg Asp Pro Lys Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala
 1235 1240 1245
 15 Leu Asp Thr Glu Ser Glu Lys Thr Val Gln Val Ala Leu Asp Lys Ala
 1250 1255 1260
 20 Arg Glu Gly Arg Thr Cys Ile Val Ile Ala His Arg Leu Ser Thr Ile
 1265 1270 1275 1280
 Gln Asn Ala Asp Ile Ile Ala Val Met Ala Gln Gly Val Val Ile Glu
 1285 1290 1295
 25 Lys Gly Thr His Glu Glu Leu Met Ala Gln Lys Gly Ala Tyr Tyr Lys
 1300 1305 1310
 30 Leu Val Thr Thr Gly Ser Pro Ile Ser
 1315 1320
 35 <210> 60
 <211> 1481
 <212> PRT
 40 <213> Homo sapiens
 <400> 60
 Met Ala Leu Arg Gly Phe Cys Ser Ala Asp Gly Ser Asp Pro Leu Trp
 1 5 10 15
 45 Asp Trp Asn Val Thr Trp Asn Thr Ser Asn Pro Asp Phe Thr Lys Cys
 20 25 30
 Phe Gln Asn Thr Val Leu Val Trp Val Pro Cys Phe Tyr Leu Trp Ala
 35 40 45
 Cys Phe Pro Phe Tyr Phe Leu Tyr Leu Ser Arg His Asp Arg Gly Tyr
 50 55 60
 55

EP 1 217 066 A1

	Ile	Gln	Met	Thr	Pro	Leu	Asn	Lys	Thr	Lys	Thr	Ala	Leu	Gly	Phe	Leu	
	65					70					75					80	
5	Leu	Trp	Ile	Val	Cys	Trp	Ala	Asp	Leu	Phe	Tyr	Ser	Phe	Trp	Glu	Arg	
					85					90					95		
	Ser	Arg	Gly	Ile	Phe	Leu	Ala	Pro	Val	Phe	Leu	Val	Ser	Pro	Thr	Leu	
10				100					105					110			
	Leu	Gly	Ile	Thr	Thr	Leu	Leu	Ala	Thr	Phe	Leu	Ile	Gln	Leu	Glu	Arg	
			115					120					125				
15	Arg	Lys	Gly	Val	Gln	Ser	Ser	Gly	Ile	Met	Leu	Thr	Phe	Trp	Leu	Val	
	130						135					140					
	Ala	Leu	Val	Cys	Ala	Leu	Ala	Ile	Leu	Arg	Ser	Lys	Ile	Met	Thr	Ala	
20	145					150				155					160		
	Leu	Lys	Glu	Asp	Ala	Gln	Val	Asp	Leu	Phe	Arg	Asp	Ile	Thr	Phe	Tyr	
				165					170					175			
25	Val	Tyr	Phe	Ser	Leu	Leu	Leu	Ile	Gln	Leu	Val	Leu	Ser	Cys	Phe	Ser	
				180					185					190			
	Asp	Arg	Ser	Pro	Leu	Phe	Ser	Glu	Thr	Ile	His	Asp	Pro	Asn	Pro	Cys	
30			195					200					205				
	Pro	Glu	Ser	Ser	Ala	Ser	Phe	Leu	Ser	Arg	Ile	Thr	Phe	Trp	Trp	Ile	
35		210					215					220					
	Thr	Gly	Leu	Ile	Val	Arg	Gly	Tyr	Arg	Gln	Pro	Leu	Glu	Gly	Ser	Asp	
	225					230				235					240		
	Leu	Trp	Ser	Leu	Asn	Lys	Glu	Asp	Thr	Ser	Glu	Gln	Val	Val	Pro	Val	
40				245					250					255			
	Leu	Val	Lys	Asn	Trp	Lys	Lys	Glu	Cys	Ala	Lys	Thr	Arg	Lys	Gln	Pro	
45				260				265					270				
	Val	Lys	Val	Val	Tyr	Ser	Ser	Lys	Asp	Pro	Ala	Gln	Pro	Lys	Glu	Ser	
				275				280					285				
50	Ser	Lys	Val	Asp	Ala	Asn	Glu	Glu	Val	Glu	Ala	Leu	Ile	Val	Lys	Ser	
	290					295						300					
	Pro	Gln	Lys	Glu	Trp	Asn	Pro	Ser	Leu	Phe	Lys	Val	Leu	Tyr	Lys	Thr	
55	305					310					315				320		

EP 1 217 066 A1

	Phe Gly Pro Tyr Phe Leu Met Ser Phe Phe Phe Lys Ala Ile His Asp	
	325	330 335
5	Leu Met Met Phe Ser Gly Pro Gln Ile Leu Lys Leu Leu Ile Lys Phe	
	340	345 350
10	Val Asn Asp Thr Lys Ala Pro Asp Trp Gln Gly Tyr Phe Tyr Thr Val	
	355	360 365
	Leu Leu Phe Val Thr Ala Cys Leu Gln Thr Leu Val Leu His Gln Tyr	
	370	375 380
15	Phe His Ile Cys Phe Val Ser Gly Met Arg Ile Lys Thr Ala Val Ile	
	385	390 395 400
20	Gly Ala Val Tyr Arg Lys Ala Leu Val Ile Thr Asn Ser Ala Arg Lys	
	405	410 415
	Ser Ser Thr Val Gly Glu Ile Val Asn Leu Met Ser Val Asp Ala Gln	
	420	425 430
25	Arg Phe Met Asp Leu Ala Thr Tyr Ile Asn Met Ile Trp Ser Ala Pro	
	435	440 445
30	Leu Gln Val Ile Leu Ala Leu Tyr Leu Leu Trp Leu Asn Leu Gly Pro	
	450	455 460
	Ser Val Leu Ala Gly Val Ala Val Met Val Leu Met Val Pro Val Asn	
	465	470 475 480
35	Ala Val Met Ala Met Lys Thr Lys Thr Tyr Gln Val Ala His Met Lys	
	485	490 495
40	Ser Lys Asp Asn Arg Ile Lys Leu Met Asn Glu Ile Leu Asn Gly Ile	
	500	505 510
	Lys Val Leu Lys Leu Tyr Ala Trp Glu Leu Ala Phe Lys Asp Lys Val	
	515	520 525
45	Leu Ala Ile Arg Gln Glu Glu Leu Lys Val Leu Lys Lys Ser Ala Tyr	
	530	535 540
50	Leu Ser Ala Val Gly Thr Phe Thr Trp Val Cys Thr Pro Phe Leu Ala	
	545	550 555 560
	Ser Val Ser Leu Lys Arg Leu Arg Ile Phe Leu Ser His Glu Glu Leu	
55	565	570 575

EP 1 217 066 A1

	Glu	Pro	Asp	Ser	Ile	Glu	Arg	Arg	Pro	Val	Lys	Asp	Gly	Gly	Gly	Thr	
				580					585				590				
5	Asn	Ser	Ile	Thr	Val	Arg	Asn	Ala	Thr	Phe	Thr	Trp	Ala	Arg	Ser	Asp	
			595					600					605				
	Pro	Pro	Thr	Leu	Asn	Gly	Ile	Thr	Phe	Ser	Ile	Pro	Glu	Gly	Ala	Leu	
10			610				615					620					
	Val	Ala	Val	Val	Gly	Gln	Val	Gly	Cys	Gly	Lys	Ser	Ser	Leu	Leu	Ser	
	625					630					635					640	
15	Ala	Leu	Leu	Ala	Glu	Met	Asp	Lys	Val	Glu	Gly	His	Val	Ala	Ile	Lys	
					645					650					655		
	Gly	Ser	Val	Ala	Tyr	Val	Pro	Gln	Gln	Ala	Trp	Ile	Gln	Asn	Asp	Ser	
20				660					665					670			
	Leu	Arg	Glu	Asn	Ile	Leu	Phe	Gly	Cys	Gln	Leu	Glu	Glu	Pro	Tyr	Tyr	
			675					680					685				
25	Arg	Ser	Val	Ile	Gln	Ala	Cys	Ala	Leu	Leu	Pro	Asp	Leu	Glu	Ile	Leu	
			690				695					700					
	Pro	Ser	Gly	Asp	Arg	Thr	Glu	Ile	Gly	Glu	Lys	Gly	Val	Asn	Leu	Ser	
30						710					715				720		
	Gly	Gly	Gln	Lys	Gln	Arg	Val	Ser	Leu	Ala	Arg	Ala	Val	Tyr	Ser	Asn	
35					725					730				735			
	Ala	Asp	Ile	Tyr	Leu	Phe	Asp	Asp	Pro	Leu	Ser	Ala	Val	Asp	Ala	His	
				740					745					750			
40	Val	Gly	Lys	His	Ile	Phe	Glu	Asn	Val	Ile	Gly	Pro	Lys	Gly	Met	Leu	
			755					760					765				
	Lys	Asn	Lys	Thr	Arg	Ile	Leu	Val	Thr	His	Ser	Met	Ser	Tyr	Leu	Pro	
45			770					775					780				
	Gln	Val	Asp	Val	Ile	Ile	Val	Met	Ser	Gly	Gly	Lys	Ile	Ser	Glu	Met	
	785					790					795				800		
50	Gly	Ser	Tyr	Gln	Glu	Leu	Leu	Ala	Arg	Asp	Gly	Ala	Phe	Ala	Glu	Phe	
				805					810						815		
	Leu	Arg	Thr	Tyr	Ala	Ser	Thr	Glu	Gln	Glu	Gln	Asp	Ala	Glu	Glu	Asn	
55				820					825					830			

EP 1 217 066 A1

	Gly Val Thr Gly Val Ser Gly Pro Gly Lys Glu Ala Lys Gln Met Glu	
	835	840 845
5	Asn Gly Met Leu Val Thr Asp Ser Ala Gly Lys Gln Leu Gln Arg Gln	
	850	855 860
10	Leu Ser Ser Ser Ser Ser Tyr Ser Gly Asp Ile Ser Arg His His Asn	
	865	870 875 880
	Ser Thr Ala Glu Leu Gln Lys Ala Glu Ala Lys Lys Glu Glu Thr Trp	
	885	890 895
15	Lys Leu Met Glu Ala Asp Lys Ala Gln Thr Gly Gln Val Lys Leu Ser	
	900	905 910
20	Val Tyr Trp Asp Tyr Met Lys Ala Ile Gly Leu Phe Ile Ser Phe Leu	
	915	920 925
	Ser Ile Phe Leu Phe Met Cys Asn His Val Ser Ala Leu Ala Ser Asn	
	930	935 940
25	Tyr Trp Leu Ser Leu Trp Thr Asp Asp Pro Ile Val Asn Gly Thr Gln	
	945	950 955 960
30	Glu His Thr Lys Val Arg Leu Ser Val Tyr Gly Ala Leu Gly Ile Ser	
	965	970 975
	Gln Gly Ile Ala Val Phe Gly Tyr Ser Met Ala Val Ser Ile Gly Gly	
	980	985 990
35	Ile Leu Ala Ser Arg Cys Leu His Val Asp Leu Leu His Ser Ile Leu	
	995	1000 1005
40	Arg Ser Pro Met Ser Phe Phe Glu Arg Thr Pro Ser Gly Asn Leu Val	
	1010	1015 1020
	Asn Arg Phe Ser Lys Glu Leu Asp Thr Val Asp Ser Met Ile Pro Glu	
	1025	1030 1035 1040
45	Val Ile Lys Met Phe Met Gly Ser Leu Phe Asn Val Ile Gly Ala Cys	
	1045	1050 1055
50	Ile Val Ile Leu Leu Ala Thr Pro Ile Ala Ala Ile Ile Ile Pro Pro	
	1060	1065 1070
	Leu Gly Leu Ile Tyr Phe Phe Val Gln Arg Phe Tyr Val Ala Ser Ser	
	1075	1080 1085
55		

EP 1 217 066 A1

	Arg Gln Leu Lys Arg Leu Glu Ser Val Ser Arg Ser Pro Val Tyr Ser	
	1090	1095 1100
5	His Phe Asn Glu Thr Leu Leu Gly Val Ser Val Ile Arg Ala Phe Glu	
	1105	1110 1115 1120
	Glu Gln Glu Arg Phe Ile His Gln Ser Asp Leu Lys Val Asp Glu Asn	
10		1125 1130 1135
	Gln Lys Ala Tyr Tyr Pro Ser Ile Val Ala Asn Arg Trp Leu Ala Val	
	1140	1145 1150
15	Arg Leu Glu Cys Val Gly Asn Cys Ile Val Leu Phe Ala Ala Leu Phe	
	1155	1160 1165
	Ala Val Ile Ser Arg His Ser Leu Ser Ala Gly Leu Val Gly Leu Ser	
20		1170 1175 1180
	Val Ser Tyr Ser Leu Gln Val Thr Thr Tyr Leu Asn Trp Leu Val Arg	
	1185	1190 1195 1200
25	Met Ser Ser Glu Met Glu Thr Asn Ile Val Ala Val Glu Arg Leu Lys	
	1205	1210 1215
	Glu Tyr Ser Glu Thr Glu Lys Glu Ala Pro Trp Gln Ile Gln Glu Thr	
30		1220 1225 1230
	Ala Pro Pro Ser Ser Trp Pro Gln Val Gly Arg Val Glu Phe Arg Asn	
35		1235 1240 1245
	Tyr Cys Leu Arg Tyr Arg Glu Asp Leu Asp Phe Val Leu Arg His Ile	
	1250	1255 1260
40	Asn Val Thr Ile Asn Gly Gly Glu Lys Val Gly Ile Val Gly Thr Gly	
	1265	1270 1275 1280
	Ala Gly Lys Ser Ser Leu Thr Leu Gly Leu Phe Arg Ile Asn Glu Ser	
45		1285 1290 1295
	Ala Glu Gly Glu Ile Ile Ile Asp Gly Ile Asn Ile Ala Lys Ile Gly	
	1300	1305 1310
50	Leu His Asp Leu Arg Phe Lys Ile Thr Ile Ile Pro Gln Asp Pro Val	
	1315	1320 1325
	Leu Phe Ser Gly Ser Leu Arg Met Asn Leu Asp Pro Phe Ser Gln Tyr	
55		1330 1335 1340

EP 1 217 066 A1

Ser Asp Glu Glu Val Trp Thr Ser Leu Glu Leu Ala His Leu Lys Asp
 1345 1350 1355 1360

5 Phe Val Ser Ala Leu Pro Asp Lys Leu Asp His Glu Cys Ala Glu Gly
 1365 1370 1375

Gly Glu Asn Leu Ser Val Gly Gln Arg Gln Leu Val Cys Leu Ala Arg
 10 1380 1385 1390

Ala Leu Leu Arg Lys Thr Lys Ile Leu Val Leu Asp Glu Ala Thr Ala
 1395 1400 1405

15 Ala Val Asp Leu Glu Thr Asp Asp Leu Ile Gln Ser Thr Ile Arg Thr
 1410 1415 1420

Gln Phe Glu Asp Cys Thr Val Leu Thr Ile Ala His Arg Leu Asn Thr
 20 1425 1430 1435 1440

Ile Met Asp Tyr Thr Arg Val Ile Val Leu Asp Lys Gly Glu Ile Gln
 1445 1450 1455

25 Glu Tyr Gly Ala Pro Ser Asp Leu Leu Gln Gln Arg Gly Leu Phe Tyr
 1460 1465 1470

Ser Met Ala Lys Asp Ala Gly Leu Val
 30 1475 1480

35 <210> 61
 <211> 1545
 <212> PRT
 <213> Homo sapiens

40 <400> 61
 Met Leu Glu Lys Phe Cys Asn Ser Thr Phe Trp Asn Ser Ser Phe Leu
 1 5 10 15

45 Asp Ser Pro Glu Ala Asp Leu Pro Leu Cys Phe Glu Gln Thr Val Leu
 20 25 30

Val Trp Ile Pro Leu Gly Phe Leu Trp Leu Leu Ala Pro Trp Gln Leu
 50 35 40 45

Leu His Val Tyr Lys Ser Arg Thr Lys Arg Ser Ser Thr Thr Lys Leu
 50 55 60

55 Tyr Leu Ala Lys Gln Val Phe Val Gly Phe Leu Leu Ile Leu Ala Ala

EP 1 217 066 A1

	65	70	75	80
5	Ile Glu Leu Ala Leu Val Leu Thr Glu Asp Ser Gly Gln Ala Thr Val	85	90	95
10	Pro Ala Val Arg Tyr Thr Asn Pro Ser Leu Tyr Leu Gly Thr Trp Leu	100	105	110
15	Leu Val Leu Leu Ile Gln Tyr Ser Arg Gln Trp Cys Val Gln Lys Asn	115	120	125
20	Ser Trp Phe Leu Ser Leu Phe Trp Ile Leu Ser Ile Leu Cys Gly Thr	130	135	140
25	Phe Gln Phe Gln Thr Leu Ile Arg Thr Leu Leu Gln Gly Asp Asn Ser	145	150	155
30	Asn Leu Ala Tyr Ser Cys Leu Phe Phe Ile Ser Tyr Gly Phe Gln Ile	165	170	175
35	Leu Ile Leu Ile Phe Ser Ala Phe Ser Glu Asn Asn Glu Ser Ser Asn	180	185	190
40	Asn Pro Ser Ser Ile Ala Ser Phe Leu Ser Ser Ile Thr Tyr Ser Trp	195	200	205
45	Tyr Asp Ser Ile Ile Leu Lys Gly Tyr Lys Arg Pro Leu Thr Leu Glu	210	215	220
50	Asp Val Trp Glu Val Asp Glu Glu Met Lys Thr Lys Thr Leu Val Ser	225	230	235
55	Lys Phe Glu Thr His Met Lys Arg Glu Leu Gln Lys Ala Arg Arg Ala	245	250	255
60	Leu Gln Arg Arg Gln Glu Lys Ser Ser Gln Gln Asn Ser Gly Ala Arg	260	265	270
65	Leu Pro Gly Leu Asn Lys Asn Gln Ser Gln Ser Gln Asp Ala Leu Val	275	280	285
70	Leu Glu Asp Val Glu Lys Lys Lys Lys Ser Gly Thr Lys Lys Asp	290	295	300
75	Val Pro Lys Ser Trp Leu Met Lys Ala Leu Phe Lys Thr Phe Tyr Met	305	310	315
80	Val Leu Leu Lys Ser Phe Leu Leu Lys Leu Val Asn Asp Ile Phe Thr			

EP 1 217 066 A1

		325		330		335
5	Phe Val Ser Pro Gln Leu Leu Lys Leu Leu Ile Ser Phe Ala Ser Asp	340		345		350
	Arg Asp Thr Tyr Leu Trp Ile Gly Tyr Leu Cys Ala Ile Leu Leu Phe	355		360		365
10	Thr Ala Ala Leu Ile Gln Ser Phe Cys Leu Gln Cys Tyr Phe Gln Leu	370		375		380
15	Cys Phe Lys Leu Gly Val Lys Val Arg Thr Ala Ile Met Ala Ser Val	385		390		395
	Tyr Lys Lys Ala Leu Thr Leu Ser Asn Leu Ala Arg Lys Glu Tyr Thr	405		410		415
20	Val Gly Glu Thr Val Asn Leu Met Ser Val Asp Ala Gln Lys Leu Met	420		425		430
25	Asp Val Thr Asn Phe Met His Met Leu Trp Ser Ser Val Leu Gln Ile	435		440		445
	Val Leu Ser Ile Phe Phe Leu Trp Arg Glu Leu Gly Pro Ser Val Leu	450		455		460
30	Ala Gly Val Gly Val Met Val Leu Val Ile Pro Ile Asn Ala Ile Leu	465		470		475
	Ser Thr Lys Ser Lys Thr Ile Gln Val Lys Asn Met Lys Asn Lys Asp	485		490		495
35	Lys Arg Leu Lys Ile Met Asn Glu Ile Leu Ser Gly Ile Lys Ile Leu	500		505		510
40	Lys Tyr Phe Ala Trp Glu Pro Ser Phe Arg Asp Gln Val Gln Asn Leu	515		520		525
45	Arg Lys Lys Glu Leu Lys Asn Leu Leu Ala Phe Ser Gln Leu Gln Cys	530		535		540
	Val Val Ile Phe Val Phe Gln Leu Thr Pro Val Leu Val Ser Val Val	545		550		555
50	Thr Phe Ser Val Tyr Val Leu Val Asp Ser Asn Asn Ile Leu Asp Ala	565		570		575
55	Gln Lys Ala Phe Thr Ser Ile Thr Leu Phe Asn Ile Leu Arg Phe Pro					

EP 1 217 066 A1

	580		585		590
5	Leu Ser Met	Leu Pro Met Met	Ile Ser Ser Met	Leu Gln Ala	Ser Val
	595		600		605
	Ser Thr Glu Arg	Leu Glu Lys Tyr	Leu Gly Gly Asp Asp	Leu Asp Thr	
	610		615		620
10	Ser Ala Ile Arg	His Asp Cys Asn Phe	Asp Lys Ala Met	Gln Phe Ser	
	625		630		640
	Glu Ala Ser Phe	Thr Trp Glu His Asp	Ser Glu Ala Thr	Val Arg Asp	
15		645		650	655
	Val Asn Leu Asp	Ile Met Ala Gly	Gln Leu Val Ala	Val Ile Gly Pro	
		660		665	670
20	Val Gly Ser Gly	Lys Ser Ser Leu	Ile Ser Ala Met	Leu Gly Glu Met	
		675		680	685
	Glu Asn Val His	Gly His Ile Thr	Ile Lys Gly Thr	Thr Ala Tyr Val	
25		690		695	700
	Pro Gln Gln Ser	Trp Ile Gln Asn Gly	Thr Ile Lys Asp	Asn Ile Leu	
30		705		710	715
	Phe Gly Thr Glu	Phe Asn Glu Lys Arg	Tyr Gln Gln Val	Leu Glu Ala	
		725		730	735
35	Cys Ala Leu Leu	Pro Asp Leu Glu	Met Leu Pro Gly	Gly Asp Leu Ala	
		740		745	750
	Glu Ile Gly Glu	Lys Gly Ile Asn	Leu Ser Gly Gly	Gln Lys Gln Arg	
40		755		760	765
	Ile Ser Leu Ala	Arg Ala Thr Tyr	Gln Asn Leu Asp	Ile Tyr Leu Leu	
		770		775	780
45	Asp Asp Pro Leu	Ser Ala Val Asp	Ala His Val Gly	Lys His Ile Phe	
		785		790	795
	Asn Lys Val Leu	Gly Pro Asn Gly	Leu Leu Lys Gly	Lys Thr Arg Leu	
50		805		810	815
	Leu Val Thr His	Ser Met His Phe	Leu Pro Gln Val	Asp Glu Ile Val	
		820		825	830
55	Val Leu Gly Asn	Gly Thr Ile Val	Glu Lys Gly Ser	Tyr Ser Ala Leu	

EP 1 217 066 A1

	835		840		845	
5	Leu Ala Lys Lys Gly Glu Phe Ala Lys Asn Leu Lys Thr Phe Leu Arg					
	850		855		860	
	His Thr Gly Pro Glu Glu Glu Ala Thr Val His Asp Gly Ser Glu Glu					
10	865		870		875	880
	Glu Asp Asp Asp Tyr Gly Leu Ile Ser Ser Val Glu Glu Ile Pro Glu					
		885		890		895
15	Asp Ala Ala Ser Ile Thr Met Arg Arg Glu Asn Ser Phe Arg Arg Thr					
		900		905		910
	Leu Ser Arg Ser Ser Arg Ser Asn Gly Arg His Leu Lys Ser Leu Arg					
20		915		920		925
	Asn Ser Leu Lys Thr Arg Asn Val Asn Ser Leu Lys Glu Asp Glu Glu					
		930		935		940
25	Leu Val Lys Gly Gln Lys Leu Ile Lys Lys Glu Phe Ile Glu Thr Gly					
	945		950		955	960
	Lys Val Lys Phe Ser Ile Tyr Leu Glu Tyr Leu Gln Ala Ile Gly Leu					
30		965		970		975
	Phe Ser Ile Phe Phe Ile Ile Leu Ala Phe Val Met Asn Ser Val Ala					
		980		985		990
35	Phe Ile Gly Ser Asn Leu Trp Leu Ser Ala Trp Thr Ser Asp Ser Lys					
		995		1000		1005
	Ile Phe Asn Ser Thr Asp Tyr Pro Ala Ser Gln Arg Asp Met Arg Val					
40		1010		1015		1020
	Gly Val Tyr Gly Ala Leu Gly Leu Ala Gln Gly Ile Phe Val Phe Ile					
	1025		1030		1035	1040
45	Ala His Phe Trp Ser Ala Phe Gly Phe Val His Ala Ser Asn Ile Leu					
		1045		1050		1055
	His Lys Gln Leu Leu Asn Asn Ile Leu Arg Ala Pro Met Arg Phe Phe					
50		1060		1065		1070
	Asp Thr Thr Pro Thr Gly Arg Ile Val Asn Arg Phe Ala Gly Asp Ile					
		1075		1080		1085
55	Ser Thr Val Asp Asp Thr Leu Pro Gln Ser Leu Arg Ser Trp Ile Thr					

EP 1 217 066 A1

	1090	1095	1100
5	Cys Phe Leu Gly Ile Ile Ser Thr Leu Val Met Ile Cys Met Ala Thr 1105	1110	1115 1120
10	Pro Val Phe Thr Ile Ile Val Ile Pro Leu Gly Ile Ile Tyr Val Ser 1125	1130	1135
	Val Gln Met Phe Tyr Val Ser Thr Ser Arg Gln Leu Arg Arg Leu Asp 1140	1145	1150
15	Ser Val Thr Arg Ser Pro Ile Tyr Ser His Phe Ser Glu Thr Val Ser 1155	1160	1165
20	Gly Leu Pro Val Ile Arg Ala Phe Glu His Gln Gln Arg Phe Leu Lys 1170	1175	1180
	His Asn Glu Val Arg Ile Asp Thr Asn Gln Lys Cys Val Phe Ser Trp 1185	1190	1195 1200
25	Ile Thr Ser Asn Arg Trp Leu Ala Ile Arg Leu Glu Leu Val Gly Asn 1205	1210	1215
30	Leu Thr Val Phe Phe Ser Ala Leu Met Met Val Ile Tyr Arg Asp Thr 1220	1225	1230
	Leu Ser Gly Asp Thr Val Gly Phe Val Leu Ser Asn Ala Leu Asn Ile 1235	1240	1245
35	Thr Gln Thr Leu Asn Trp Leu Val Arg Met Thr Ser Glu Ile Glu Thr 1250	1255	1260
40	Asn Ile Val Ala Val Glu Arg Ile Thr Glu Tyr Thr Lys Val Glu Asn 1265	1270	1275 1280
	Glu Ala Pro Trp Val Thr Asp Lys Arg Pro Pro Pro Asp Trp Pro Ser 1285	1290	1295
45	Lys Gly Lys Ile Gln Phe Asn Asn Tyr Gln Val Arg Tyr Arg Pro Glu 1300	1305	1310
50	Leu Asp Leu Val Leu Arg Gly Ile Thr Cys Asp Ile Gly Ser Met Glu 1315	1320	1325
	Lys Ile Gly Val Val Gly Arg Thr Gly Ala Gly Lys Ser Ser Leu Thr 1330	1335	1340
55	Asn Cys Leu Phe Arg Ile Leu Glu Ala Ala Gly Gly Gln Ile Ile Ile		

EP 1 217 066 A1

	1345	1350	1355	1360
5	Asp Gly Val Asp Ile Ala Ser Ile Gly Leu His Asp Leu Arg Glu Lys			
	1365	1370	1375	
10	Leu Thr Ile Ile Pro Gln Asp Pro Ile Leu Phe Ser Gly Ser Leu Arg			
	1380	1385	1390	
15	Met Asn Leu Asp Pro Phe Asn Asn Tyr Ser Asp Glu Glu Ile Trp Lys			
	1395	1400	1405	
20	Ala Leu Glu Leu Ala His Leu Lys Ser Phe Val Ala Ser Leu Gln Leu			
	1410	1415	1420	
25	Gly Leu Ser His Glu Val Thr Glu Ala Gly Gly Asn Leu Ser Ile Gly			
	1425	1430	1435	1440
30	Gln Arg Gln Leu Leu Cys Leu Gly Arg Ala Leu Leu Arg Lys Ser Lys			
	1445	1450	1455	
35	Ile Leu Val Leu Asp Glu Ala Thr Ala Ala Val Asp Leu Glu Thr Asp			
	1460	1465	1470	
40	Asn Leu Ile Gln Thr Thr Ile Gln Asn Glu Phe Ala His Cys Thr Val			
	1475	1480	1485	
45	Ile Thr Ile Ala His Arg Leu His Thr Ile Met Asp Ser Asp Lys Val			
	1490	1495	1500	
50	Met Val Leu Asp Asn Gly Lys Ile Ile Glu Cys Gly Ser Pro Glu Glu			
	1505	1510	1515	1520
55	Leu Leu Gln Ile Pro Gly Pro Phe Tyr Phe Met Ala Lys Glu Ala Gly			
	1525	1530	1535	
	Ile Glu Asn Val Asn Ser Thr Lys Phe			
	1540	1545		
	<210> 62			
	<211> 1527			
	<212> PRT			
	<213> Homo sapiens			
	<400> 62			
	Met Asp Ala Leu Cys Gly Ser Gly Glu Leu Gly Ser Lys Phe Trp Asp			
	1	5	10	15

EP 1 217 066 A1

5	Ser Asn Leu Ser Val His Thr Glu Asn Pro Asp Leu Thr Pro Cys Phe	20	25	30
	Gln Asn Ser Leu Leu Ala Trp Val Pro Cys Ile Tyr Leu Trp Val Ala	35	40	45
10	Leu Pro Cys Tyr Leu Leu Tyr Leu Arg His His Cys Arg Gly Tyr Ile	50	55	60
	Ile Leu Ser His Leu Ser Lys Leu Lys Met Val Leu Gly Val Leu Leu	65	70	75
15				80
	Trp Cys Val Ser Trp Ala Asp Leu Phe Tyr Ser Phe His Gly Leu Val	85	90	95
20	His Gly Arg Ala Pro Ala Pro Val Phe Phe Val Thr Pro Leu Val Val	100	105	110
	Gly Val Thr Met Leu Leu Ala Thr Leu Leu Ile Gln Tyr Glu Arg Leu	115	120	125
25				
	Gln Gly Val Gln Ser Ser Gly Val Leu Ile Ile Phe Trp Phe Leu Cys	130	135	140
30	Val Val Cys Ala Ile Val Pro Phe Arg Ser Lys Ile Leu Leu Ala Lys	145	150	155
				160
35	Ala Glu Gly Glu Ile Ser Asp Pro Phe Arg Phe Thr Thr Phe Tyr Ile	165	170	175
	His Phe Ala Leu Val Leu Ser Ala Leu Ile Leu Ala Cys Phe Arg Glu	180	185	190
40				
	Lys Pro Pro Phe Phe Ser Ala Lys Asn Val Asp Pro Asn Pro Tyr Pro	195	200	205
45	Glu Thr Ser Ala Gly Phe Leu Ser Arg Leu Phe Phe Trp Trp Phe Thr	210	215	220
	Lys Met Ala Ile Tyr Gly Tyr Arg His Pro Leu Glu Glu Lys Asp Leu	225	230	235
50				240
	Trp Ser Leu Lys Glu Glu Asp Arg Ser Gln Met Val Val Gln Gln Leu	245	250	255
55	Leu Glu Ala Trp Arg Lys Gln Glu Lys Gln Thr Ala Arg His Lys Ala	260	265	270

EP 1 217 066 A1

5	Ser	Ala	Ala	Pro	Gly	Lys	Asn	Ala	Ser	Gly	Glu	Asp	Glu	Val	Leu	Leu	275	280	285
	Gly	Ala	Arg	Pro	Arg	Pro	Arg	Lys	Pro	Ser	Phe	Leu	Lys	Ala	Leu	Leu	290	295	300
10	Ala	Thr	Phe	Gly	Ser	Ser	Phe	Leu	Ile	Ser	Ala	Cys	Phe	Lys	Leu	Ile	305	310	315
	Gln	Asp	Leu	Leu	Ser	Phe	Ile	Asn	Pro	Gln	Leu	Leu	Ser	Ile	Leu	Ile	325	330	335
15	Arg	Phe	Ile	Ser	Asn	Pro	Met	Ala	Pro	Ser	Trp	Trp	Gly	Phe	Leu	Val	340	345	350
20	Ala	Gly	Leu	Met	Phe	Leu	Cys	Ser	Met	Met	Gln	Ser	Leu	Ile	Leu	Gln	355	360	365
25	His	Tyr	Tyr	His	Tyr	Ile	Phe	Val	Thr	Gly	Val	Lys	Phe	Arg	Thr	Gly	370	375	380
	Ile	Met	Gly	Val	Ile	Tyr	Arg	Lys	Ala	Leu	Val	Ile	Thr	Asn	Ser	Val	385	390	395
30	Lys	Arg	Ala	Ser	Thr	Val	Gly	Glu	Ile	Val	Asn	Leu	Met	Ser	Val	Asp	405	410	415
35	Ala	Gln	Arg	Phe	Met	Asp	Leu	Ala	Pro	Phe	Leu	Asn	Leu	Leu	Trp	Ser	420	425	430
	Ala	Pro	Leu	Gln	Ile	Ile	Leu	Ala	Ile	Tyr	Phe	Leu	Trp	Gln	Asn	Leu	435	440	445
40	Gly	Pro	Ser	Val	Leu	Ala	Gly	Val	Ala	Phe	Met	Val	Leu	Leu	Ile	Pro	450	455	460
45	Leu	Asn	Gly	Ala	Val	Ala	Val	Lys	Met	Arg	Ala	Phe	Gln	Val	Lys	Gln	465	470	475
	Met	Lys	Leu	Lys	Asp	Ser	Arg	Ile	Lys	Leu	Met	Ser	Glu	Ile	Leu	Asn	485	490	495
50	Gly	Ile	Lys	Val	Leu	Lys	Leu	Tyr	Ala	Trp	Glu	Pro	Ser	Phe	Leu	Lys	500	505	510
55	Gln	Val	Glu	Gly	Ile	Arg	Gln	Gly	Glu	Leu	Gln	Leu	Leu	Arg	Thr	Ala	515	520	525

EP 1 217 066 A1

5	Ala Tyr Leu His Thr Thr Thr Thr Phe Thr Trp Met Cys Ser Pro Phe	530	535	540
	Leu Val Thr Leu Ile Thr Leu Trp Val Tyr Val Tyr Val Asp Pro Asn	545	550	555 560
10	Asn Val Leu Asp Ala Glu Lys Ala Phe Val Ser Val Ser Leu Phe Asn	565	570	575
	Ile Leu Arg Leu Pro Leu Asn Met Leu Pro Gln Leu Ile Ser Asn Leu	580	585	590
15	Thr Gln Ala Ser Val Ser Leu Lys Arg Ile Gln Gln Phe Leu Ser Gln	595	600	605
20	Glu Glu Leu Asp Pro Gln Ser Val Glu Arg Lys Thr Ile Ser Pro Gly	610	615	620
	Tyr Ala Ile Thr Ile His Ser Gly Thr Phe Thr Trp Ala Gln Asp Leu	625	630	635 640
25	Pro Pro Thr Leu His Ser Leu Asp Ile Gln Val Pro Lys Gly Ala Leu	645	650	655
30	Val Ala Val Val Gly Pro Val Gly Cys Gly Lys Ser Ser Leu Val Ser	660	665	670
	Ala Leu Leu Gly Glu Met Glu Lys Leu Glu Gly Lys Val His Met Lys	675	680	685
35	Gly Ser Val Ala Tyr Val Pro Gln Gln Ala Trp Ile Gln Asn Cys Thr	690	695	700
40	Leu Gln Glu Asn Val Leu Phe Gly Lys Ala Leu Asn Pro Lys Arg Tyr	705	710	715 720
	Gln Gln Thr Leu Glu Ala Cys Ala Leu Leu Ala Asp Leu Glu Met Leu	725	730	735
45	Pro Gly Gly Asp Gln Thr Glu Ile Gly Glu Lys Gly Ile Asn Leu Ser	740	745	750
50	Gly Gly Gln Arg Gln Arg Val Ser Leu Ala Arg Ala Val Tyr Ser Asp	755	760	765
	Ala Asp Ile Phe Leu Leu Asp Asp Pro Leu Ser Ala Val Asp Ser His	770	775	780

EP 1 217 066 A1

	Val	Ala	Lys	His	Ile	Phe	Asp	His	Val	Ile	Gly	Pro	Glu	Gly	Val	Leu	
	785						790					795				800	
5																	
	Ala	Gly	Lys	Thr	Arg	Val	Leu	Val	Thr	His	Gly	Ile	Ser	Phe	Leu	Pro	
					805					810					815		
10																	
	Gln	Thr	Asp	Phe	Ile	Ile	Val	Leu	Ala	Asp	Gly	Gln	Val	Ser	Glu	Met	
				820					825					830			
15																	
	Gly	Pro	Tyr	Pro	Ala	Leu	Leu	Gln	Arg	Asn	Gly	Ser	Phe	Ala	Asn	Phe	
			835					840					845				
20																	
	Leu	Cys	Asn	Tyr	Ala	Pro	Asp	Glu	Asp	Gln	Gly	His	Leu	Glu	Asp	Ser	
		850					855					860					
25																	
	Trp	Thr	Ala	Leu	Glu	Gly	Ala	Glu	Asp	Lys	Glu	Ala	Leu	Leu	Ile	Glu	
	865				870					875					880		
30																	
	Asp	Thr	Leu	Ser	Asn	His	Thr	Asp	Leu	Thr	Asp	Asn	Asp	Pro	Val	Thr	
					885					890					895		
35																	
	Tyr	Val	Val	Gln	Lys	Gln	Phe	Met	Arg	Gln	Leu	Ser	Ala	Leu	Ser	Ser	
				900					905					910			
40																	
	Asp	Gly	Glu	Gly	Gln	Gly	Arg	Pro	Val	Pro	Arg	Arg	His	Leu	Gly	Pro	
		915						920					925				
45																	
	Ser	Glu	Lys	Val	Gln	Val	Thr	Glu	Ala	Lys	Ala	Asp	Gly	Ala	Leu	Thr	
		930					935					940					
50																	
	Gln	Glu	Glu	Lys	Ala	Ala	Ile	Gly	Thr	Val	Glu	Leu	Ser	Val	Phe	Trp	
	945			950						955					960		
55																	
	Asp	Tyr	Ala	Lys	Ala	Val	Gly	Leu	Cys	Thr	Thr	Leu	Ala	Ile	Cys	Leu	
				965					970					975			
60																	
	Leu	Tyr	Val	Gly	Gln	Ser	Ala	Ala	Ala	Ile	Gly	Ala	Asn	Val	Trp	Leu	
		980						985					990				
65																	
	Ser	Ala	Trp	Thr	Asn	Asp	Ala	Met	Ala	Asp	Ser	Arg	Gln	Asn	Asn	Thr	
		995					1000					1005					
70																	
	Ser	Leu	Arg	Leu	Gly	Val	Tyr	Ala	Ala	Leu	Gly	Ile	Leu	Gln	Gly	Phe	
		1010					1015					1020					
75																	
	Leu	Val	Met	Leu	Ala	Ala	Met	Ala	Met	Ala	Ala	Gly	Gly	Ile	Gln	Ala	
	1025			1030						1035				1040			

EP 1 217 066 A1

	Ala Arg Val Leu His Gln Ala Leu Leu His Asn Lys Ile Arg Ser Pro	
	1045	1050 1055
5	Gln Ser Phe Phe Asp Thr Thr Pro Ser Gly Arg Ile Leu Asn Cys Phe	
	1060	1065 1070
10	Ser Lys Asp Ile Tyr Val Val Asp Glu Val Leu Ala Pro Val Ile Leu	
	1075	1080 1085
15	Met Leu Leu Asn Ser Phe Phe Asn Ala Ile Ser Thr Leu Val Val Ile	
	1090	1095 1100
	Met Ala Ser Thr Pro Leu Phe Thr Val Val Ile Leu Pro Leu Ala Val	
	1105	1110 1115 1120
20	Leu Tyr Thr Leu Val Gln Arg Phe Tyr Ala Ala Thr Ser Arg Gln Leu	
	1125	1130 1135
25	Lys Arg Leu Glu Ser Val Ser Arg Ser Pro Ile Tyr Ser His Phe Ser	
	1140	1145 1150
	Glu Thr Val Thr Gly Ala Ser Val Ile Arg Ala Tyr Asn Arg Ser Arg	
	1155	1160 1165
30	Asp Phe Glu Ile Ile Ser Asp Thr Lys Val Asp Ala Asn Gln Arg Ser	
	1170	1175 1180
35	Cys Tyr Pro Tyr Ile Ile Ser Asn Arg Trp Leu Ser Ile Gly Val Glu	
	1185	1190 1195 1200
	Phe Val Gly Asn Cys Val Val Leu Phe Ala Ala Leu Phe Ala Val Ile	
	1205	1210 1215
40	Gly Arg Ser Ser Leu Asn Pro Gly Leu Val Gly Leu Ser Val Ser Tyr	
	1220	1225 1230
45	Ser Leu Gln Val Thr Phe Ala Leu Asn Trp Met Ile Arg Met Met Ser	
	1235	1240 1245
50	Asp Leu Glu Ser Asn Ile Val Ala Val Glu Arg Val Lys Glu Tyr Ser	
	1250	1255 1260
	Lys Thr Glu Thr Glu Ala Pro Trp Val Val Glu Gly Ser Arg Pro Pro	
	1265	1270 1275 1280
55	Glu Gly Trp Pro Pro Arg Gly Glu Val Glu Phe Arg Asn Tyr Ser Val	
	1285	1290 1295

EP 1 217 066 A1

5	Arg Tyr Arg Pro Gly Leu Asp Leu Val Leu Arg Asp Leu Ser Leu His	1300	1305	1310
	Val His Gly Gly Glu Lys Val Gly Ile Val Gly Arg Thr Gly Ala Gly	1315	1320	1325
10	Lys Ser Ser Met Thr Leu Cys Leu Phe Arg Ile Leu Glu Ala Ala Lys	1330	1335	1340
15	Gly Glu Ile Arg Ile Asp Gly Leu Asn Val Ala Asp Ile Gly Leu His	1345	1350	1355
	Asp Leu Arg Ser Gln Leu Thr Ile Ile Pro Gln Asp Pro Ile Leu Phe	1365	1370	1375
20	Ser Gly Thr Leu Arg Met Asn Leu Asp Pro Phe Gly Ser Tyr Ser Glu	1380	1385	1390
25	Glu Asp Ile Trp Trp Ala Leu Glu Leu Ser His Leu His Thr Phe Val	1395	1400	1405
	Ser Ser Gln Pro Ala Gly Leu Asp Phe Gln Cys Ser Glu Gly Gly Glu	1410	1415	1420
30	Asn Leu Ser Val Gly Gln Arg Gln Leu Val Cys Leu Ala Arg Ala Leu	1425	1430	1435
	Leu Arg Lys Ser Arg Ile Leu Val Leu Asp Glu Ala Thr Ala Ala Ile	1445	1450	1455
35	Asp Leu Glu Thr Asp Asn Leu Ile Gln Ala Thr Ile Arg Thr Gln Phe	1460	1465	1470
40	Asp Thr Cys Thr Val Leu Thr Ile Ala His Arg Leu Asn Thr Ile Met	1475	1480	1485
45	Asp Tyr Thr Arg Val Leu Val Leu Asp Lys Gly Val Val Ala Glu Phe	1490	1495	1500
50	Asp Ser Pro Ala Asn Leu Ile Ala Ala Arg Gly Ile Phe Tyr Gly Met	1505	1510	1515
	Ala Arg Asp Ala Gly Leu Ala	1525		

55

EP 1 217 066 A1

<210> 63
 <211> 1325
 <212> PRT
 <213> Homo sapiens

<400> 63
 Met Leu Pro Val Tyr Gln Glu Val Lys Pro Asn Pro Leu Gln Asp Ala
 1 5 10 15
 Asn Ile Cys Ser Arg Val Phe Phe Trp Trp Leu Asn Pro Leu Phe Lys
 20 25 30
 Ile Gly His Lys Arg Arg Leu Glu Glu Asp Asp Met Tyr Ser Val Leu
 35 40 45
 Pro Glu Asp Arg Ser Gln His Leu Gly Glu Glu Leu Gln Gly Phe Trp
 50 55 60
 Asp Lys Glu Val Leu Arg Ala Glu Asn Asp Ala Gln Lys Pro Ser Leu
 65 70 75 80
 Thr Arg Ala Ile Ile Lys Cys Tyr Trp Lys Ser Tyr Leu Val Leu Gly
 85 90 95
 Ile Phe Thr Leu Ile Glu Glu Ser Ala Lys Val Ile Gln Pro Ile Phe
 100 105 110
 Leu Gly Lys Ile Ile Asn Tyr Phe Glu Asn Tyr Asp Pro Met Asp Ser
 115 120 125
 Val Ala Leu Asn Thr Ala Tyr Ala Tyr Ala Thr Val Leu Thr Phe Cys
 130 135 140
 Thr Leu Ile Leu Ala Ile Leu His His Leu Tyr Phe Tyr His Val Gln
 145 150 155 160
 Cys Ala Gly Met Arg Leu Arg Val Ala Met Cys His Met Ile Tyr Arg
 165 170 175
 Lys Ala Leu Arg Leu Ser Asn Met Ala Met Gly Lys Thr Thr Thr Gly
 180 185 190
 Gln Ile Val Asn Leu Leu Ser Asn Asp Val Asn Lys Phe Asp Gln Val
 195 200 205
 Thr Val Phe Leu His Phe Leu Trp Ala Gly Pro Leu Gln Ala Ile Ala
 210 215 220

EP 1 217 066 A1

	Val Thr Ala Leu Leu Trp Met Glu Ile Gly Ile Ser Cys Leu Ala Gly	
	225	230 235 240
5	Met Ala Val Leu Ile Ile Leu Leu Pro Leu Gln Ser Cys Phe Gly Lys	
		245 250 255
10	Leu Phe Ser Ser Leu Arg Ser Lys Thr Ala Thr Phe Thr Asp Ala Arg	
		260 265 270
	Ile Arg Thr Met Asn Glu Val Ile Thr Gly Ile Arg Ile Ile Lys Met	
15		275 280 285
	Tyr Ala Trp Glu Lys Ser Phe Ser Asn Leu Ile Thr Asn Leu Arg Lys	
		290 295 300
20	Lys Glu Ile Ser Lys Ile Leu Arg Ser Ser Cys Leu Arg Gly Met Asn	
		305 310 315 320
	Leu Ala Ser Phe Phe Ser Ala Ser Lys Ile Ile Val Phe Val Thr Phe	
25		325 330 335
	Thr Thr Tyr Val Leu Leu Gly Ser Val Ile Thr Ala Ser Arg Val Phe	
		340 345 350
30	Val Ala Val Thr Leu Tyr Gly Ala Val Arg Leu Thr Val Thr Leu Phe	
		355 360 365
	Phe Pro Ser Ala Ile Glu Arg Val Ser Glu Ala Ile Val Ser Ile Arg	
35		370 375 380
	Arg Ile Gln Thr Phe Leu Leu Leu Asp Glu Ile Ser Gln Arg Asn Arg	
		385 390 395 400
40	Gln Leu Pro Ser Asp Gly Lys Lys Met Val His Val Gln Asp Phe Thr	
		405 410 415
	Ala Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr Leu Gln Gly Leu Ser	
45		420 425 430
	Phe Thr Val Arg Pro Gly Glu Leu Leu Ala Val Val Gly Pro Val Gly	
		435 440 445
50	Ala Gly Lys Ser Ser Leu Leu Ser Ala Val Leu Gly Glu Leu Ala Pro	
		450 455 460
55	Ser His Gly Leu Val Ser Val His Gly Arg Ile Ala Tyr Val Ser Gln	
		465 470 475 480

EP 1 217 066 A1

	Gln	Pro	Trp	Val	Phe	Ser	Gly	Thr	Leu	Arg	Ser	Asn	Ile	Leu	Phe	Gly	
					485					490					495		
5	Lys	Lys	Tyr	Glu	Lys	Glu	Arg	Tyr	Glu	Lys	Val	Ile	Lys	Ala	Cys	Ala	
				500					505					510			
10	Leu	Lys	Lys	Asp	Leu	Gln	Leu	Leu	Glu	Asp	Gly	Asp	Leu	Thr	Val	Ile	
				515				520					525				
15	Gly	Asp	Arg	Gly	Thr	Thr	Leu	Ser	Gly	Gly	Gln	Lys	Ala	Arg	Val	Asn	
				530			535					540					
	Leu	Ala	Arg	Ala	Val	Tyr	Gln	Asp	Ala	Asp	Ile	Tyr	Leu	Leu	Asp	Asp	
	545					550					555				560		
20	Pro	Leu	Ser	Ala	Val	Asp	Ala	Glu	Val	Ser	Arg	His	Leu	Phe	Glu	Leu	
					565					570					575		
25	Cys	Ile	Cys	Gln	Ile	Leu	His	Glu	Lys	Ile	Thr	Ile	Leu	Val	Thr	His	
				580					585					590			
	Gln	Leu	Gln	Tyr	Leu	Lys	Ala	Ala	Ser	Gln	Ile	Leu	Ile	Leu	Lys	Asp	
				595				600					605				
30	Gly	Lys	Met	Val	Gln	Lys	Gly	Thr	Tyr	Thr	Glu	Phe	Leu	Lys	Ser	Gly	
				610			615					620					
35	Ile	Asp	Phe	Gly	Ser	Leu	Leu	Lys	Lys	Asp	Asn	Glu	Glu	Ser	Glu	Gln	
	625					630					635				640		
	Pro	Pro	Val	Pro	Gly	Thr	Pro	Thr	Leu	Arg	Asn	Arg	Thr	Phe	Ser	Glu	
					645					650					655		
40	Ser	Ser	Val	Trp	Ser	Gln	Gln	Ser	Ser	Arg	Pro	Ser	Leu	Lys	Asp	Gly	
				660					665					670			
45	Ala	Leu	Glu	Ser	Gln	Asp	Thr	Glu	Asn	Val	Pro	Val	Thr	Leu	Ser	Glu	
				675				680					685				
50	Glu	Asn	Arg	Ser	Glu	Gly	Lys	Val	Gly	Phe	Gln	Ala	Tyr	Lys	Asn	Tyr	
		690					695					700					
	Phe	Arg	Ala	Gly	Ala	His	Trp	Ile	Val	Phe	Ile	Phe	Leu	Ile	Leu	Leu	
	705					710					715				720		
55	Asn	Thr	Ala	Ala	Gln	Val	Ala	Tyr	Val	Leu	Gln	Asp	Trp	Trp	Leu	Ser	
					725					730					735		

EP 1 217 066 A1

Tyr Trp Ala Asn Lys Gln Ser Met Leu Asn Val Thr Val Asn Gly Gly
 740 745 750
 5
 Gly Asn Val Thr Glu Lys Leu Asp Leu Asn Trp Tyr Leu Gly Ile Tyr
 755 760 765
 10
 Ser Gly Leu Thr Val Ala Thr Val Leu Phe Gly Ile Ala Arg Ser Leu
 770 775 780
 Leu Val Phe Tyr Val Leu Val Asn Ser Ser Gln Thr Leu His Asn Lys
 785 790 795 800
 15
 Met Phe Glu Ser Ile Leu Lys Ala Pro Val Leu Phe Phe Asp Arg Asn
 805 810 815
 20
 Pro Ile Gly Arg Ile Leu Asn Arg Phe Ser Lys Asp Ile Gly His Leu
 820 825 830
 Asp Asp Leu Leu Pro Leu Thr Phe Leu Asp Phe Ile Gln Thr Leu Leu
 835 840 845
 25
 Gln Val Val Gly Val Val Ser Val Ala Val Ala Val Ile Pro Trp Ile
 850 855 860
 30
 Ala Ile Pro Leu Val Pro Leu Gly Ile Ile Phe Ile Phe Leu Arg Arg
 865 870 875 880
 Tyr Phe Leu Glu Thr Ser Arg Asp Val Lys Arg Leu Glu Ser Thr Thr
 885 890 895
 35
 Arg Ser Pro Val Phe Ser His Leu Ser Ser Ser Leu Gln Gly Leu Trp
 900 905 910
 40
 Thr Ile Arg Ala Tyr Lys Ala Glu Glu Arg Cys Gln Glu Leu Phe Asp
 915 920 925
 Ala His Gln Asp Leu His Ser Glu Ala Trp Phe Leu Phe Leu Thr Thr
 930 935 940
 45
 Ser Arg Trp Phe Ala Val Arg Leu Asp Ala Ile Cys Ala Met Phe Val
 945 950 955 960
 50
 Ile Ile Val Ala Phe Gly Ser Leu Ile Leu Ala Lys Thr Leu Asp Ala
 965 970 975
 55
 Gly Gln Val Gly Leu Ala Leu Ser Tyr Ala Leu Thr Leu Met Gly Met
 980 985 990

EP 1 217 066 A1

Phe Gln Trp Cys Val Arg Gln Ser Ala Glu Val Glu Asn Met Met Ile
 995 1000 1005
 5
 Ser Val Glu Arg Val Ile Glu Tyr Thr Asp Leu Glu Lys Glu Ala Pro
 1010 1015 1020
 Trp Glu Tyr Gln Lys Arg Pro Pro Pro Ala Trp Pro His Glu Gly Val
 10 1025 1030 1035 1040
 Ile Ile Phe Asp Asn Val Asn Phe Met Tyr Ser Pro Gly Gly Pro Leu
 15 1045 1050 1055
 Val Leu Lys His Leu Thr Ala Leu Ile Lys Ser Gln Glu Lys Val Gly
 1060 1065 1070
 Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser Leu Ile Ser Ala Leu
 20 1075 1080 1085
 Phe Arg Leu Ser Glu Pro Glu Gly Lys Ile Trp Ile Asp Lys Ile Leu
 25 1090 1095 1100
 Thr Thr Glu Ile Gly Leu His Asp Leu Arg Lys Lys Met Ser Ile Ile
 1105 1110 1115 1120
 Pro Gln Glu Pro Val Leu Phe Thr Gly Thr Met Arg Lys Asn Leu Asp
 30 1125 1130 1135
 Pro Phe Lys Glu His Thr Asp Glu Glu Leu Trp Asn Ala Leu Gln Glu
 35 1140 1145 1150
 Val Gln Leu Lys Glu Thr Ile Glu Asp Leu Pro Gly Lys Met Asp Thr
 1155 1160 1165
 Glu Leu Ala Glu Ser Gly Ser Asn Phe Ser Val Gly Gln Arg Gln Leu
 40 1170 1175 1180
 Val Cys Leu Ala Arg Ala Ile Leu Arg Lys Asn Gln Ile Leu Ile Ile
 45 1185 1190 1195 1200
 Asp Glu Ala Thr Ala Asn Val Asp Pro Arg Thr Asp Glu Leu Ile Gln
 1205 1210 1215
 Lys Lys Ile Arg Glu Lys Phe Ala His Cys Thr Val Leu Thr Ile Ala
 50 1220 1225 1230
 His Arg Leu Asn Thr Ile Ile Asp Ser Asp Lys Ile Met Val Leu Asp
 55 1235 1240 1245

EP 1 217 066 A1

Ser Gly Arg Leu Lys Glu Tyr Asp Glu Pro Tyr Val Leu Leu Gln Asn
 1250 1255 1260
 5
 Lys Glu Ser Leu Phe Tyr Lys Met Val Gln Gln Leu Gly Lys Ala Glu
 1265 1270 1275 1280
 10
 Ala Ala Ala Leu Thr Glu Thr Ala Lys Gln Val Tyr Phe Lys Arg Asn
 1285 1290 1295
 Tyr Pro His Ile Gly His Thr Asp His Met Val Thr Asn Thr Ser Asn
 1300 1305 1310
 15
 Gly Gln Pro Ser Thr Leu Thr Ile Phe Glu Thr Ala Leu
 1315 1320 1325
 20
 <210> 64
 <211> 1437
 <212> PRT
 25
 <213> Homo sapiens
 <400> 64
 Met Lys Asp Ile Asp Ile Gly Lys Glu Tyr Ile Ile Pro Ser Pro Gly
 30 1 5 10 15
 Tyr Arg Ser Val Arg Glu Arg Thr Ser Thr Ser Gly Thr His Arg Asp
 20 25 30
 35
 Arg Glu Asp Ser Lys Phe Arg Arg Thr Arg Pro Leu Glu Cys Gln Asp
 35 40 45
 40
 Ala Leu Glu Thr Ala Ala Arg Ala Glu Gly Leu Ser Leu Asp Ala Ser
 50 55 60
 Met His Ser Gln Leu Arg Ile Leu Asp Glu Glu His Pro Lys Gly Lys
 65 70 75 80
 45
 Tyr His His Gly Leu Ser Ala Leu Lys Pro Ile Arg Thr Thr Ser Lys
 85 90 95
 50
 His Gln His Pro Val Asp Asn Ala Gly Leu Phe Ser Cys Met Thr Phe
 100 105 110
 Ser Trp Leu Ser Ser Leu Ala Arg Val Ala His Lys Lys Gly Glu Leu
 115 120 125
 55
 Ser Met Glu Asp Val Trp Ser Leu Ser Lys His Glu Ser Ser Asp Val

EP 1 217 066 A1

	130	135	140
5	Asn Cys Arg Arg Leu Glu Arg Leu Trp Gln Glu Glu Leu Asn Glu Val 145	150	155 160
10	Gly Pro Asp Ala Ala Ser Leu Arg Arg Val Val Trp Ile Phe Cys Arg 165	170	175
	Thr Arg Leu Ile Leu Ser Ile Val Cys Leu Met Ile Thr Gln Leu Ala 180	185	190
15	Gly Phe Ser Gly Pro Ala Phe Met Val Lys His Leu Leu Glu Tyr Thr 195	200	205
20	Gln Ala Thr Glu Ser Asn Leu Gln Tyr Ser Leu Leu Leu Val Leu Gly 210	215	220
	Leu Leu Leu Thr Glu Ile Val Arg Ser Trp Ser Leu Ala Leu Thr Trp 225	230	235 240
25	Ala Leu Asn Tyr Arg Thr Gly Val Arg Leu Arg Gly Ala Ile Leu Thr 245	250	255
30	Met Ala Phe Lys Lys Ile Leu Lys Leu Lys Asn Ile Lys Glu Lys Ser 260	265	270
	Leu Gly Glu Leu Ile Asn Ile Cys Ser Asn Asp Gly Gln Arg Met Phe 275	280	285
35	Glu Ala Ala Ala Val Gly Ser Leu Leu Ala Gly Gly Pro Val Val Ala 290	295	300
40	Ile Leu Gly Met Ile Tyr Asn Val Ile Ile Leu Gly Pro Thr Gly Phe 305	310	315 320
	Leu Gly Ser Ala Val Phe Ile Leu Phe Tyr Pro Ala Met Met Phe Ala 325	330	335
45	Ser Arg Leu Thr Ala Tyr Phe Arg Arg Lys Cys Val Ala Ala Thr Asp 340	345	350
50	Glu Arg Val Gln Lys Met Asn Glu Val Leu Thr Tyr Ile Lys Phe Ile 355	360	365
	Lys Met Tyr Ala Trp Val Lys Ala Phe Ser Gln Ser Val Gln Lys Ile 370	375	380
55	Arg Glu Glu Glu Arg Arg Ile Leu Glu Lys Ala Gly Tyr Phe Gln Gly		

EP 1 217 066 A1

	385		390		395		400
5	Ile Thr Val Gly Val Ala Pro Ile Val Val Val Ile Ala Ser Val Val	405		410		415	
10	Thr Phe Ser Val His Met Thr Leu Gly Phe Asp Leu Thr Ala Ala Gln	420		425		430	
	Ala Phe Thr Val Val Thr Val Phe Asn Ser Met Thr Phe Ala Leu Lys	435		440		445	
15	Val Thr Pro Phe Ser Val Lys Ser Leu Ser Glu Ala Ser Val Ala Val	450		455		460	
20	Asp Arg Phe Lys Ser Leu Phe Leu Met Glu Glu Val His Met Ile Lys	465		470		475	480
	Asn Lys Pro Ala Ser Pro His Ile Lys Ile Glu Met Lys Asn Ala Thr	485		490		495	
25	Leu Ala Trp Asp Ser Ser His Ser Ser Ile Gln Asn Ser Pro Lys Leu	500		505		510	
30	Thr Pro Lys Met Lys Lys Asp Lys Arg Ala Ser Arg Gly Lys Lys Glu	515		520		525	
	Lys Val Arg Gln Leu Gln Arg Thr Glu His Gln Ala Val Leu Ala Glu	530		535		540	
35	Gln Lys Gly His Leu Leu Leu Asp Ser Asp Glu Arg Pro Ser Pro Glu	545		550		555	560
40	Glu Glu Glu Gly Lys His Ile His Leu Gly His Leu Arg Leu Gln Arg	565		570		575	
	Thr Leu His Ser Ile Asp Leu Glu Ile Gln Glu Gly Lys Leu Val Gly	580		585		590	
45	Ile Cys Gly Ser Val Gly Ser Gly Lys Thr Ser Leu Ile Ser Ala Ile	595		600		605	
50	Leu Gly Gln Met Thr Leu Leu Glu Gly Ser Ile Ala Ile Ser Gly Thr	610		615		620	
	Phe Ala Tyr Val Ala Gln Gln Ala Trp Ile Leu Asn Ala Thr Leu Arg	625		630		635	640
55	Asp Asn Ile Leu Phe Gly Lys Glu Tyr Asp Glu Glu Arg Tyr Asn Ser						

EP 1 217 066 A1

	645	650	655
5	Val Leu Asn Ser Cys Cys Leu Arg	Pro Asp Leu Ala Ile Leu Pro Ser	
	660	665	670
10	Ser Asp Leu Thr Glu Ile Gly Glu Arg Gly Ala Asn Leu Ser Gly Gly		
	675	680	685
15	Gln Arg Gln Arg Ile Ser Leu Ala Arg Ala Leu Tyr Ser Asp Arg Ser		
	690	695	700
20	Ile Tyr Ile Leu Asp Asp Pro Leu Ser Ala Leu Asp Ala His Val Gly		
	705	710	715
	720		
	Asn His Ile Phe Asn Ser Ala Ile Arg Lys His Leu Lys Ser Lys Thr		
	725	730	735
25	Val Leu Phe Val Thr His Gln Leu Gln Tyr Leu Val Asp Cys Asp Glu		
	740	745	750
30	Val Ile Phe Met Lys Glu Gly Cys Ile Thr Glu Arg Gly Thr His Glu		
	755	760	765
	Glu Leu Met Asn Leu Asn Gly Asp Tyr Ala Thr Ile Phe Asn Asn Leu		
	770	775	780
35	Leu Leu Gly Glu Thr Pro Pro Val Glu Ile Asn Ser Lys Lys Glu Thr		
	785	790	795
	800		
40	Ser Gly Ser Gln Lys Lys Ser Gln Asp Lys Gly Pro Lys Thr Gly Ser		
	805	810	815
	Val Lys Lys Glu Lys Ala Val Lys Pro Glu Glu Gly Gln Leu Val Gln		
	820	825	830
45	Leu Glu Glu Lys Gly Gln Gly Ser Val Pro Trp Ser Val Tyr Gly Val		
	835	840	845
50	Tyr Ile Gln Ala Ala Gly Gly Pro Leu Ala Phe Leu Val Ile Met Ala		
	850	855	860
	Leu Phe Met Leu Asn Val Gly Ser Thr Ala Phe Ser Thr Trp Trp Leu		
	865	870	875
	880		
55	Ser Tyr Trp Ile Lys Gln Gly Ser Gly Asn Thr Thr Val Thr Arg Gly		
	885	890	895
	Asn Glu Thr Ser Val Ser Asp Ser Met Lys Asp Asn Pro His Met Gln		

EP 1 217 066 A1

	900	905	910
5	Tyr Tyr Ala Ser Ile Tyr Ala Leu Ser Met Ala Val Met Leu Ile Leu 915 920 925		
10	Lys Ala Ile Arg Gly Val Val Phe Val Lys Gly Thr Leu Arg Ala Ser 930 935 940		
15	Ser Arg Leu His Asp Glu Leu Phe Arg Arg Ile Leu Arg Ser Pro Met 945 950 955 960		
20	Lys Phe Phe Asp Thr Thr Pro Thr Gly Arg Ile Leu Asn Arg Phe Ser 965 970 975		
25	Lys Asp Met Asp Glu Val Asp Val Arg Leu Pro Phe Gln Ala Glu Met 980 985 990		
30	Phe Ile Gln Asn Val Ile Leu Val Phe Phe Cys Val Gly Met Ile Ala 995 1000 1005		
35	Gly Val Phe Pro Trp Phe Leu Val Ala Val Gly Pro Leu Val Ile Leu 1010 1015 1020		
40	Phe Ser Val Leu His Ile Val Ser Arg Val Leu Ile Arg Glu Leu Lys 1025 1030 1035 1040		
45	Arg Leu Asp Asn Ile Thr Gln Ser Pro Phe Leu Ser His Ile Thr Ser 1045 1050 1055		
50	Ser Ile Gln Gly Leu Ala Thr Ile His Ala Tyr Asn Lys Gly Gln Glu 1060 1065 1070		
55	Phe Leu His Arg Tyr Gln Glu Leu Leu Asp Asp Asn Gln Ala Pro Phe 1075 1080 1085		
	Phe Leu Phe Thr Cys Ala Met Arg Trp Leu Ala Val Arg Leu Asp Leu 1090 1095 1100		
	Ile Ser Ile Ala Leu Ile Thr Thr Thr Gly Leu Met Ile Val Leu Met 1105 1110 1115 1120		
	His Gly Gln Ile Pro Pro Ala Tyr Ala Gly Leu Ala Ile Ser Tyr Ala 1125 1130 1135		
	Val Gln Leu Thr Gly Leu Phe Gln Phe Thr Val Arg Leu Ala Ser Glu 1140 1145 1150		
	Thr Glu Ala Arg Phe Thr Ser Val Glu Arg Ile Asn His Tyr Ile Lys		

EP 1 217 066 A1

	1155	1160	1165
5	Thr Leu Ser Leu Glu Ala Pro Ala Arg Ile Lys Asn Lys Ala Pro Ser 1170	1175	1180
10	Pro Asp Trp Pro Gln Glu Gly Glu Val Thr Phe Glu Asn Ala Glu Met 1185	1190	1195 1200
	Arg Tyr Arg Glu Asn Leu Pro Leu Val Leu Lys Lys Val Ser Phe Thr 1205	1210	1215
15	Ile Lys Pro Lys Glu Lys Ile Gly Ile Val Gly Arg Thr Gly Ser Gly 1220	1225	1230
20	Lys Ser Ser Leu Gly Met Ala Leu Phe Arg Leu Val Glu Leu Ser Gly 1235	1240	1245
	Gly Cys Ile Lys Ile Asp Gly Val Arg Ile Ser Asp Ile Gly Leu Ala 1250	1255	1260
25	Asp Leu Arg Ser Lys Leu Ser Ile Ile Pro Gln Glu Pro Val Leu Phe 1265	1270	1275 1280
30	Ser Gly Thr Val Arg Ser Asn Leu Asp Pro Phe Asn Gln Tyr Thr Glu 1285	1290	1295
	Asp Gln Ile Trp Asp Ala Leu Glu Arg Thr His Met Lys Glu Cys Ile 1300	1305	1310
35	Ala Gln Leu Pro Leu Lys Leu Glu Ser Glu Val Met Glu Asn Gly Asp 1315	1320	1325
40	Asn Phe Ser Val Gly Glu Arg Gln Leu Leu Cys Ile Ala Arg Ala Leu 1330	1335	1340
	Leu Arg His Cys Lys Ile Leu Ile Leu Asp Glu Ala Thr Ala Ala Met 1345	1350	1355 1360
45	Asp Thr Glu Thr Asp Leu Leu Ile Gln Glu Thr Ile Arg Glu Ala Phe 1365	1370	1375
50	Ala Asp Cys Thr Met Leu Thr Ile Ala His Arg Leu His Thr Val Leu 1380	1385	1390
	Gly Ser Asp Arg Ile Met Val Leu Ala Gln Gly Gln Val Val Glu Phe 1395	1400	1405
55	Asp Thr Pro Ser Val Leu Leu Ser Asn Asp Ser Ser Arg Phe Tyr Ala		

EP 1 217 066 A1

	1410	1415	1420
5	Met Phe Ala Ala Ala Glu Asn Lys Val Ala Val Lys Gly		
	1425	1430	1435
10	<210> 65		
	<211> 1503		
	<212> PRT		
	<213> Homo sapiens		
15	<400> 65		
	Met Ala Ala Pro Ala Glu Pro Cys Ala Gly Gln Gly Val Trp Asn Gln		
	1	5	10 15
20	Thr Glu Pro Glu Pro Ala Ala Thr Ser Leu Leu Ser Leu Cys Phe Leu		
	20	25	30
25	Arg Thr Ala Gly Val Trp Val Pro Pro Met Tyr Leu Trp Val Leu Gly		
	35	40	45
	Pro Ile Tyr Leu Leu Phe Ile His His His Gly Arg Gly Tyr Leu Trp		
	50	55	60
30	Met Ser Pro Leu Phe Lys Ala Lys Met Val Leu Gly Phe Ala Leu Ile		
	65	70	75 80
35	Val Leu Cys Thr Ser Ser Val Ala Val Ala Leu Trp Lys Ile Gln Gln		
	85	90	95
	Gly Thr Pro Glu Ala Pro Glu Phe Leu Ile His Pro Thr Val Trp Leu		
	100	105	110
40	Thr Thr Met Ser Phe Ala Val Phe Leu Ile His Thr Glu Arg Lys Lys		
	115	120	125
45	Gly Val Gln Ser Ser Gly Val Leu Phe Gly Tyr Trp Leu Leu Cys Phe		
	130	135	140
	Val Leu Pro Ala Thr Asn Ala Ala Gln Gln Ala Ser Gly Ala Gly Phe		
	145	150	155 160
50	Gln Ser Asp Pro Val Arg His Leu Ser Thr Tyr Leu Cys Leu Ser Leu		
	165	170	175
55	Val Val Ala Gln Phe Val Leu Ser Cys Leu Ala Asp Gln Pro Pro Phe		
	180	185	190

EP 1 217 066 A1

5	Phe	Pro	Glu	Asp	Pro	Gln	Gln	Ser	Asn	Pro	Cys	Pro	Glu	Thr	Gly	Ala	195	200	205	
	Ala	Phe	Pro	Ser	Lys	Ala	Thr	Phe	Trp	Trp	Val	Ser	Gly	Leu	Val	Trp	210	215	220	
10	Arg	Gly	Tyr	Arg	Arg	Pro	Leu	Arg	Pro	Lys	Asp	Leu	Trp	Ser	Leu	Gly	225	230	235	240
15	Arg	Glu	Asn	Ser	Ser	Glu	Glu	Leu	Val	Ser	Arg	Leu	Glu	Lys	Glu	Trp	245	250	255	
	Met	Arg	Asn	Arg	Ser	Ala	Ala	Arg	Arg	His	Asn	Lys	Ala	Ile	Ala	Phe	260	265	270	
20	Lys	Arg	Lys	Gly	Gly	Ser	Gly	Met	Lys	Ala	Pro	Glu	Thr	Glu	Pro	Phe	275	280	285	
25	Leu	Arg	Gln	Glu	Gly	Ser	Gln	Trp	Arg	Pro	Leu	Leu	Lys	Ala	Ile	Trp	290	295	300	
	Gln	Val	Phe	His	Ser	Thr	Phe	Leu	Leu	Gly	Thr	Leu	Ser	Leu	Ile	Ile	305	310	315	320
30	Ser	Asp	Val	Phe	Arg	Phe	Thr	Val	Pro	Lys	Leu	Leu	Ser	Leu	Phe	Leu	325	330	335	
35	Glu	Phe	Ile	Gly	Asp	Pro	Lys	Pro	Pro	Ala	Trp	Lys	Gly	Tyr	Leu	Leu	340	345	350	
	Ala	Val	Leu	Met	Phe	Leu	Ser	Ala	Cys	Leu	Gln	Thr	Leu	Phe	Glu	Gln	355	360	365	
40	Gln	Asn	Met	Tyr	Arg	Leu	Lys	Val	Leu	Gln	Met	Arg	Leu	Arg	Ser	Ala	370	375	380	
45	Ile	Thr	Gly	Leu	Val	Tyr	Arg	Lys	Val	Leu	Ala	Leu	Ser	Ser	Gly	Ser	385	390	395	400
	Arg	Lys	Ala	Ser	Ala	Val	Gly	Asp	Val	Val	Asn	Leu	Val	Ser	Val	Asp	405	410	415	
50	Val	Gln	Arg	Leu	Thr	Glu	Ser	Val	Leu	Tyr	Leu	Asn	Gly	Leu	Trp	Leu	420	425	430	
55	Pro	Leu	Val	Trp	Ile	Val	Val	Cys	Phe	Val	Tyr	Leu	Trp	Gln	Leu	Leu	435	440	445	

EP 1 217 066 A1

5	Gly Pro Ser Ala Leu Thr Ala Ile Ala Val Phe Leu Ser Leu Leu Pro	450	455	460
	Leu Asn Phe Phe Ile Ser Lys Lys Arg Asn His His Gln Glu Glu Gln	465	470	475 480
10	Met Arg Gln Lys Asp Ser Arg Ala Arg Leu Thr Ser Ser Ile Leu Arg	485	490	495
15	Asn Ser Lys Thr Ile Lys Phe His Gly Trp Glu Gly Ala Phe Leu Asp	500	505	510
	Arg Val Leu Gly Ile Arg Gly Gln Glu Leu Gly Ala Leu Arg Thr Ser	515	520	525
20	Gly Leu Leu Phe Ser Val Ser Leu Val Ser Phe Gln Val Ser Thr Phe	530	535	540
25	Leu Val Ala Leu Val Val Phe Ala Val His Thr Leu Val Ala Glu Asn	545	550	555 560
	Ala Met Asn Ala Glu Lys Ala Phe Val Thr Leu Thr Val Leu Asn Ile	565	570	575
30	Leu Asn Lys Ala Gln Ala Phe Leu Pro Phe Ser Ile His Ser Leu Val	580	585	590
35	Gln Ala Arg Val Ser Phe Asp Arg Leu Val Thr Phe Leu Cys Leu Glu	595	600	605
	Glu Val Asp Pro Gly Val Val Asp Ser Ser Ser Ser Gly Ser Ala Ala	610	615	620
40	Gly Lys Asp Cys Ile Thr Ile His Ser Ala Thr Phe Ala Trp Ser Gln	625	630	635 640
45	Glu Ser Pro Pro Cys Leu His Arg Ile Asn Leu Thr Val Pro Gln Gly	645	650	655
	Cys Leu Leu Ala Val Val Gly Pro Val Gly Ala Gly Lys Ser Ser Leu	660	665	670
50	Leu Ser Ala Leu Leu Gly Glu Leu Ser Lys Val Glu Gly Phe Val Ser	675	680	685
55	Ile Glu Gly Ala Val Ala Tyr Val Pro Gln Glu Ala Trp Val Gln Asn	690	695	700

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

RECEIVED

MAR 31 2006
4 of 5

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
BARRY L. DAVISON
2600 CENTURY SQUARE
1501 FOURTH AVENUE
SEATTLE, WA 98101-1688

Date of mailing
(day/month/year) **29 MAR 2006**

Applicant's or agent's file reference
55382-28

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US05/14668

International filing date
(day/month/year) 27 April 2005 (27.04.2005)

Applicant
ILLUMIGEN BIOSCIENCES, INC.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Searching Authority, 1211 Geneva 20, Switzerland.

For what? Detailed instructions, see the accompanying sheet.

2. ☐ The applicant declares that the international search report and the declaration under Article 17 of the PCT have been established and that the declaration under Article 17 of the PCT and the international search report are transmitted herewith.

3. ☐ In respect of the international payment of an additional fee(s) under Rule 40.2, the applicant is notified that:
the protest, together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer

David Humphrey

Telephone No. (571) 272-6000

Form PCT/ISA/220 (January 2004)

See notes on accompanying sheet

EP 1 217 066 A1

5 Thr Ser Val Val Glu Asn Val Cys Phe Gly Gln Glu Leu Asp Pro Pro
 705 710 715 720
 Trp Leu Glu Arg Val Leu Glu Ala Cys Ala Leu Gln Pro Asp Val Asp
 725 730 735
 10 Ser Phe Pro Glu Gly Ile His Thr Ser Ile Gly Glu Gln Gly Met Asn
 740 745 750
 Leu Ser Gly Gly Gln Lys Gln Arg Leu Ser Leu Ala Arg Ala Val Tyr
 15 755 760 765
 Arg Lys Ala Ala Val Tyr Leu Leu Asp Asp Pro Leu Ala Ala Leu Asp
 770 775 780
 20 Ala His Val Gly Gln His Val Phe Asn Gln Val Ile Gly Pro Gly Gly
 785 790 795 800
 Leu Leu Gln Gly Thr Thr Arg Ile Leu Val Thr His Ala Leu His Ile
 25 805 810 815
 Leu Pro Gln Ala Asp Trp Ile Ile Val Leu Ala Asn Gly Ala Ile Ala
 820 825 830
 30 Glu Met Gly Ser Tyr Gln Glu Leu Leu Gln Arg Lys Gly Ala Leu Val
 835 840 845
 Cys Leu Leu Asp Gln Ala Arg Gln Pro Gly Asp Arg Gly Glu Gly Glu
 35 850 855 860
 Thr Glu Pro Gly Thr Ser Thr Lys Asp Pro Arg Gly Thr Ser Ala Gly
 40 865 870 875 880
 Arg Arg Pro Glu Leu Arg Arg Glu Arg Ser Ile Lys Ser Val Pro Glu
 885 890 895
 45 Lys Asp Arg Thr Thr Ser Glu Ala Gln Thr Glu Val Pro Leu Asp Asp
 900 905 910
 Pro Asp Arg Ala Gly Trp Pro Ala Gly Lys Asp Ser Ile Gln Tyr Gly
 915 920 925
 50 Arg Val Lys Ala Thr Val His Leu Ala Tyr Leu Arg Ala Val Gly Thr
 930 935 940
 Pro Leu Cys Leu Tyr Ala Leu Phe Leu Phe Leu Cys Gln Gln Val Ala
 55 945 950 955 960

EP 1 217 066 A1

5	Ser Phe Cys Arg Gly Tyr Trp Leu Ser Leu Trp Ala Asp Asp Pro Ala	965	970	975
	Val Gly Gly Gln Gln Thr Gln Ala Ala Leu Arg Gly Gly Ile Phe Gly	980	985	990
10	Leu Leu Gly Cys Leu Gln Ala Ile Gly Leu Phe Ala Ser Met Ala Ala	995	1000	1005
	Val Leu Leu Gly Gly Ala Arg Ala Ser Arg Leu Leu Phe Gln Arg Leu	1010	1015	1020
15	Leu Trp Asp Val Val Arg Ser Pro Ile Ser Phe Phe Glu Arg Thr Pro	1025	1030	1035
	Ile Gly His Leu Leu Asn Arg Phe Ser Lys Glu Thr Asp Thr Val Asp	1045	1050	1055
20	Val Asp Ile Pro Asp Lys Leu Arg Ser Leu Leu Met Tyr Ala Phe Gly	1060	1065	1070
	Leu Leu Glu Val Ser Leu Val Val Ala Val Ala Thr Pro Leu Ala Thr	1075	1080	1085
25	Val Ala Ile Leu Pro Leu Phe Leu Leu Tyr Ala Gly Phe Gln Ser Leu	1090	1095	1100
	Tyr Val Val Ser Ser Cys Gln Leu Arg Arg Leu Glu Ser Ala Ser Tyr	1105	1110	1115
30	Ser Ser Val Cys Ser His Met Ala Glu Thr Phe Gln Gly Ser Thr Val	1125	1130	1135
	Val Arg Ala Phe Arg Thr Gln Ala Pro Phe Val Ala Gln Asn Asn Ala	1140	1145	1150
35	Arg Val Asp Glu Ser Gln Arg Ile Ser Phe Pro Arg Leu Val Ala Asp	1155	1160	1165
	Arg Trp Leu Ala Ala Asn Val Glu Leu Leu Gly Asn Gly Leu Val Phe	1170	1175	1180
40	Ala Ala Ala Thr Cys Ala Val Leu Ser Lys Ala His Leu Ser Ala Gly	1185	1190	1195
	Leu Val Gly Phe Ser Val Ser Ala Ala Leu Gln Val Thr Gln Thr Leu	1205	1210	1215
45				
50				
55				

EP 1 217 066 A1

5 Gln Trp Val Val Arg Asn Trp Thr Asp Leu Glu Asn Ser Ile Val Ser
 1220 1225 1230
 Val Glu Arg Met Gln Asp Tyr Ala Trp Thr Pro Lys Glu Ala Pro Trp
 1235 1240 1245
 10 Arg Leu Pro Thr Cys Ala Ala Gln Pro Pro Trp Pro Gln Gly Gly Gln
 1250 1255 1260
 Ile Glu Phe Arg Asp Phe Gly Leu Arg Tyr Arg Pro Glu Leu Pro Leu
 15 1265 1270 1275 1280
 Ala Val Gln Gly Val Ser Phe Lys Ile His Ala Gly Glu Lys Val Gly
 1285 1290 1295
 20 Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser Leu Ala Ser Gly Leu
 1300 1305 1310
 Leu Arg Leu Gln Glu Ala Ala Glu Gly Gly Ile Trp Ile Asp Gly Val
 25 1315 1320 1325
 Pro Ile Ala His Val Gly Leu His Thr Leu Arg Ser Arg Ile Ser Ile
 1330 1335 1340
 30 Ile Pro Gln Asp Pro Ile Leu Phe Pro Gly Ser Leu Arg Met Asn Leu
 1345 1350 1355 1360
 Asp Leu Leu Gln Glu His Ser Asp Glu Ala Ile Trp Ala Ala Leu Glu
 35 1365 1370 1375
 Thr Val Gln Leu Lys Ala Leu Val Ala Ser Leu Pro Gly Gln Leu Gln
 1380 1385 1390
 40 Tyr Lys Cys Ala Asp Arg Gly Glu Asp Leu Ser Val Gly Gln Lys Gln
 1395 1400 1405
 Leu Leu Cys Leu Ala Arg Ala Leu Leu Arg Lys Thr Gln Ile Leu Ile
 45 1410 1415 1420
 Leu Asp Glu Ala Thr Ala Ala Val Asp Pro Gly Thr Glu Leu Gln Met
 50 1425 1430 1435 1440
 Gln Ala Met Leu Gly Ser Trp Phe Ala Gln Cys Thr Val Leu Leu Ile
 1445 1450 1455
 55 Ala His Arg Leu Arg Ser Val Met Asp Cys Ala Arg Val Leu Val Met
 1460 1465 1470

EP 1 217 066 A1

Asp Lys Gly Gln Val Ala Glu Ser Gly Ser Pro Ala Gln Leu Leu Ala
 1475 1480 1485
 5
 Gln Lys Gly Leu Phe Tyr Arg Leu Ala Gln Glu Ser Gly Leu Val
 1490 1495 1500
 10
 <210> 66
 <211> 1480
 <212> PRT
 <213> Homo sapiens
 15
 <400> 66
 Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser Lys Leu Phe
 1 5 10 15
 Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg Gln Arg Leu
 20 25 30
 25
 Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser Ala Asp Asn
 35 40 45
 30
 Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu Ala Ser Lys
 50 55 60
 Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe Phe Trp Arg
 65 70 75 80
 35
 Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val Thr Lys Ala
 85 90 95
 40
 Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr Asp Pro Asp
 100 105 110
 Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile Gly Leu Cys
 115 120 125
 45
 Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala Ile Phe Gly
 130 135 140
 50
 Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe Ser Leu Ile
 145 150 155 160
 Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp Lys Ile Ser
 165 170 175
 55

EP 1 217 066 A1

	Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn Lys Phe Asp	
	180	185 190
5	Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro Leu Gln Val	
	195	200 205
10	Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala Ser Ala Phe	
	210	215 220
15	Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln Ala Gly Leu	
	225	230 235 240
	Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly Lys Ile Ser	
	245	250 255
20	Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile Gln Ser Val	
	260	265 270
25	Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile Glu Asn Leu	
	275	280 285
	Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr Val Arg Tyr	
	290	295 300
30	Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val Val Phe Leu	
	305	310 315 320
35	Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu Arg Lys Ile	
	325	330 335
	Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala Val Thr Arg	
	340	345 350
40	Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu Gly Ala Ile	
	355	360 365
45	Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys Thr Leu Glu	
	370	375 380
50	Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val Thr Ala Phe	
	385	390 395 400
	Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys Gln Asn Asn	
	405	410 415
55	Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe Phe Ser Asn	
	420	425 430

EP 1 217 066 A1

	Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn Phe Lys Ile	
	435	440 445
5	Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly Ala Gly Lys	
	450	455 460
10	Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro Ser Glu Gly	
	465	470 475 480
15	Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln Phe Ser Trp	
		485 490 495
	Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly Val Ser Tyr	
		500 505 510
20	Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln Leu Glu Glu	
		515 520 525
25	Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu Gly Glu Gly	
	530	535 540
	Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser Leu Ala Arg	
	545	550 555 560
30	Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser Pro Phe Gly	
		565 570 575
35	Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser Cys Val Cys	
	580	585 590
	Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser Lys Met Glu	
	595	600 605
40	His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu Gly Ser Ser	
	610	615 620
45	Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln Pro Asp Phe	
	625	630 635 640
50	Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe Ser Ala Glu	
		645 650 655
	Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe Ser Leu Glu	
		660 665 670
55	Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln Ser Phe Lys	
	675	680 685

EP 1 217 066 A1

	Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile Leu Asn Pro	
	690	695 700
5	Ile Asn Ser Ile Arg Lys Phe Ser Ile Val Gln Lys Thr Pro Leu Gln	
	705	710 715 720
10	Met Asn Gly Ile Glu Glu Asp Ser Asp Glu Pro Leu Glu Arg Arg Leu	
		725 730 735
15	Ser Leu Val Pro Asp Ser Glu Gln Gly Glu Ala Ile Leu Pro Arg Ile	
		740 745 750
	Ser Val Ile Ser Thr Gly Pro Thr Leu Gln Ala Arg Arg Arg Gln Ser	
	755	760 765
20	Val Leu Asn Leu Met Thr His Ser Val Asn Gln Gly Gln Asn Ile His	
	770	775 780
25	Arg Lys Thr Thr Ala Ser Thr Arg Lys Val Ser Leu Ala Pro Gln Ala	
	785	790 795 800
	Asn Leu Thr Glu Leu Asp Ile Tyr Ser Arg Arg Leu Ser Gln Glu Thr	
		805 810 815
30	Gly Leu Glu Ile Ser Glu Glu Ile Asn Glu Glu Asp Leu Lys Glu Cys	
		820 825 830
35	Phe Phe Asp Asp Met Glu Ser Ile Pro Ala Val Thr Thr Trp Asn Thr	
		835 840 845
	Tyr Leu Arg Tyr Ile Thr Val His Lys Ser Leu Ile Phe Val Leu Ile	
	850	855 860
40	Trp Cys Leu Val Ile Phe Leu Ala Glu Val Ala Ala Ser Leu Val Val	
	865	870 875 880
45	Leu Trp Leu Leu Gly Asn Thr Pro Leu Gln Asp Lys Gly Asn Ser Thr	
		885 890 895
	His Ser Arg Asn Asn Ser Tyr Ala Val Ile Ile Thr Ser Thr Ser Ser	
		900 905 910
50	Tyr Tyr Val Phe Tyr Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala	
	915	920 925
55	Met Gly Phe Phe Arg Gly Leu Pro Leu Val His Thr Leu Ile Thr Val	
	930	935 940

EP 1 217 066 A1

	Ser Lys Ile Leu His His Lys Met Leu His Ser Val Leu Gln Ala Pro	
	945	950 955 960
5	Met Ser Thr Leu Asn Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe	
		965 970 975
10	Ser Lys Asp Ile Ala Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe	
		980 985 990
15	Asp Phe Ile Gln Leu Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val	
		995 1000 1005
	Ala Val Leu Gln Pro Tyr Ile Phe Val Ala Thr Val Pro Val Ile Val	
		1010 1015 1020
20	Ala Phe Ile Met Leu Arg Ala Tyr Phe Leu Gln Thr Ser Gln Gln Leu	
		1025 1030 1035 1040
25	Lys Gln Leu Glu Ser Glu Gly Arg Ser Pro Ile Phe Thr His Leu Val	
		1045 1050 1055
	Thr Ser Leu Lys Gly Leu Trp Thr Leu Arg Ala Phe Gly Arg Gln Pro	
		1060 1065 1070
30	Tyr Phe Glu Thr Leu Phe His Lys Ala Leu Asn Leu His Thr Ala Asn	
		1075 1080 1085
35	Trp Phe Leu Tyr Leu Ser Thr Leu Arg Trp Phe Gln Met Arg Ile Glu	
		1090 1095 1100
40	Met Ile Phe Val Ile Phe Phe Ile Ala Val Thr Phe Ile Ser Ile Leu	
		1105 1110 1115 1120
	Thr Thr Gly Glu Gly Glu Gly Arg Val Gly Ile Ile Leu Thr Leu Ala	
		1125 1130 1135
45	Met Asn Ile Met Ser Thr Leu Gln Trp Ala Val Asn Ser Ser Ile Asp	
		1140 1145 1150
50	Val Asp Ser Leu Met Arg Ser Val Ser Arg Val Phe Lys Phe Ile Asp	
		1155 1160 1165
	Met Pro Thr Glu Gly Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn	
		1170 1175 1180
55	Gly Gln Leu Ser Lys Val Met Ile Ile Glu Asn Ser His Val Lys Lys	
		1185 1190 1195 1200

EP 1 217 066 A1

5	Asp Asp Ile Trp Pro Ser Gly Gly Gln Met Thr Val Lys Asp Leu Thr	1205	1210	1215
	Ala Lys Tyr Thr Glu Gly Gly Asn Ala Ile Leu Glu Asn Ile Ser Phe	1220	1225	1230
10	Ser Ile Ser Pro Gly Gln Arg Val Gly Leu Leu Gly Arg Thr Gly Ser	1235	1240	1245
15	Gly Lys Ser Thr Leu Leu Ser Ala Phe Leu Arg Leu Leu Asn Thr Glu	1250	1255	1260
	Gly Glu Ile Gln Ile Asp Gly Val Ser Trp Asp Ser Ile Thr Leu Gln	1265	1270	1275
20	Gln Trp Arg Lys Ala Phe Gly Val Ile Pro Gln Lys Val Phe Ile Phe	1285	1290	1295
25	Ser Gly Thr Phe Arg Lys Asn Leu Asp Pro Tyr Glu Gln Trp Ser Asp	1300	1305	1310
	Gln Glu Ile Trp Lys Val Ala Asp Glu Val Gly Leu Arg Ser Val Ile	1315	1320	1325
30	Glu Gln Phe Pro Gly Lys Leu Asp Phe Val Leu Val Asp Gly Gly Cys	1330	1335	1340
35	Val Leu Ser His Gly His Lys Gln Leu Met Cys Leu Ala Arg Ser Val	1345	1350	1355
	Leu Ser Lys Ala Lys Ile Leu Leu Leu Asp Glu Pro Ser Ala His Leu	1365	1370	1375
40	Asp Pro Val Thr Tyr Gln Ile Ile Arg Arg Thr Leu Lys Gln Ala Phe	1380	1385	1390
45	Ala Asp Cys Thr Val Ile Leu Cys Glu His Arg Ile Glu Ala Met Leu	1395	1400	1405
50	Glu Cys Gln Gln Phe Leu Val Ile Glu Glu Asn Lys Val Arg Gln Tyr	1410	1415	1420
	Asp Ser Ile Gln Lys Leu Leu Asn Glu Arg Ser Leu Phe Arg Gln Ala	1425	1430	1435
55	Ile Ser Pro Ser Asp Arg Val Lys Leu Phe Pro His Arg Asn Ser Ser	1445	1450	1455

EP 1 217 066 A1

Lys Cys Lys Ser Lys Pro Gln Ile Ala Ala Leu Lys Glu Glu Thr Glu
 1460 1465 1470
 5
 Glu Glu Val Gln Asp Thr Arg Leu
 1475 1480
 10
 <210> 67
 <211> 1581
 <212> PRT
 15 <213> Homo sapiens
 <400> 67
 Met Pro Leu Ala Phe Cys Gly Ser Glu Asn His Ser Ala Ala Tyr Arg
 1 5 10 15
 20 Val Asp Gln Gly Val Leu Asn Asn Gly Cys Phe Val Asp Ala Leu Asn
 20 25 30
 25 Val Val Pro His Val Phe Leu Leu Phe Ile Thr Phe Pro Ile Leu Phe
 35 40 45
 30 Ile Gly Trp Gly Ser Gln Ser Ser Lys Val His Ile His His Ser Thr
 50 55 60
 Trp Leu His Phe Pro Gly His Asn Leu Arg Trp Ile Leu Thr Phe Met
 65 70 75 80
 35 Leu Leu Phe Val Leu Val Cys Glu Ile Ala Glu Gly Ile Leu Ser Asp
 85 90 95
 40 Gly Val Thr Glu Ser His His Leu His Leu Tyr Met Pro Ala Gly Met
 100 105 110
 Ala Phe Met Ala Ala Val Thr Ser Val Val Tyr Tyr His Asn Ile Glu
 115 120 125
 45 Thr Ser Asn Phe Pro Lys Leu Leu Ile Ala Leu Leu Val Tyr Trp Thr
 130 135 140
 50 Leu Ala Phe Ile Thr Lys Thr Ile Lys Phe Val Lys Leu Leu Asp His
 145 150 155 160
 Ala Ile Gly Phe Ser Gln Leu Arg Phe Cys Leu Thr Gly Leu Leu Val
 165 170 175
 55 Ile Leu Tyr Gly Met Leu Leu Leu Val Glu Val Asn Val Ile Arg Val

EP 1 217 066 A1

	180	185	190
5	Arg Arg Tyr Ile Phe Phe Lys Thr Pro Arg Glu Val Lys Pro Pro Glu 195 200 205		
10	Asp Leu Gln Asp Leu Gly Val Arg Phe Leu Gln Pro Phe Val Asn Leu 210 215 220		
	Pro Ser Lys Gly Thr Tyr Trp Trp Met Asn Ala Phe Ile Lys Thr Ala 225 230 235 240		
15	His Lys Lys Pro Ile Asp Leu Arg Ala Ile Gly Lys Leu Pro Ile Val 245 250 255		
20	Met Arg Ala Leu Thr Asn Tyr Gln Arg Leu Cys Glu Ala Phe Asp Ala 260 265 270		
	Gln Val Arg Lys Asp Ile Gln Gly Thr Gln Gly Ala Arg Ala Ile Trp 275 280 285		
25	Gln Ala Leu Ser His Ala Phe Gly Arg Arg Leu Val Leu Ser Ser Thr 290 295 300		
30	Phe Arg Ile Leu Ala Asp Leu Leu Gly Phe Ala Gly Pro Leu Cys Ile 305 310 315 320		
	Phe Gly Ile Val Asp His Leu Gly Lys Glu Asn Asp Val Phe Gln Pro 325 330 335		
35	Lys Thr Gln Phe Leu Gly Val Tyr Phe Val Ser Ser Gln Glu Phe Leu 340 345 350		
40	Ala Asn Ala Tyr Val Leu Ala Val Leu Leu Phe Leu Ala Leu Leu Leu 355 360 365		
	Gln Arg Thr Phe Leu Gln Ala Ser Tyr Tyr Val Ala Ile Glu Thr Gly 370 375 380		
45	Ile Asn Leu Arg Gly Ala Ile Gln Thr Lys Ile Tyr Asn Lys Ile Met 385 390 395 400		
50	His Leu Ser Thr Ser Asn Leu Ser Met Gly Glu Met Thr Ala Gly Gln 405 410 415		
	Ile Cys Asn Leu Val Ala Ile Asp Thr Asn Gln Leu Met Trp Phe Phe 420 425 430		
55	Phe Leu Cys Pro Asn Leu Trp Ala Met Pro Val Gln Ile Ile Val Gly		

EP 1 217 066 A1

	435	440	445
5	Val Ile Leu Leu Tyr Tyr Ile Leu Gly Val Ser Ala Leu Ile Gly Ala 450	455	460
10	Ala Val Ile Ile Leu Leu Ala Pro Val Gln Tyr Phe Val Ala Thr Lys 465	470	475 480
	Leu Ser Gln Ala Gln Arg Ser Thr Leu Glu Tyr Ser Asn Glu Arg Leu 485	490	495
15	Lys Gln Thr Asn Glu Met Leu Arg Gly Ile Lys Leu Leu Lys Leu Tyr 500	505	510
20	Ala Trp Glu Asn Ile Phe Arg Thr Arg Val Glu Thr Thr Arg Arg Lys 515	520	525
	Glu Met Thr Ser Leu Arg Ala Phe Ala Ile Tyr Thr Ser Ile Ser Ile 530	535	540
25	Phe Met Asn Thr Ala Ile Pro Ile Ala Ala Val Leu Ile Thr Phe Val 545	550	555 560
30	Gly His Val Ser Phe Phe Lys Glu Ala Asp Phe Ser Pro Ser Val Ala 565	570	575
	Phe Ala Ser Leu Ser Leu Phe His Ile Leu Val Thr Pro Leu Phe Leu 580	585	590
35	Leu Ser Ser Val Val Arg Ser Thr Val Lys Ala Leu Val Ser Val Gln 595	600	605
40	Lys Leu Ser Glu Phe Leu Ser Ser Ala Glu Ile Arg Glu Glu Gln Cys 610	615	620
	Ala Pro His Glu Pro Thr Pro Gln Gly Pro Ala Ser Lys Tyr Gln Ala 625	630	635 640
45	Val Pro Leu Arg Val Val Asn Arg Lys Arg Pro Ala Arg Glu Asp Cys 645	650	655
50	Arg Gly Leu Thr Gly Pro Leu Gln Ser Leu Val Pro Ser Ala Asp Gly 660	665	670
	Asp Ala Asp Asn Cys Cys Val Gln Ile Met Gly Gly Tyr Phe Thr Trp 675	680	685
55	Thr Pro Asp Gly Ile Pro Thr Leu Ser Asn Ile Thr Ile Arg Ile Pro		

EP 1 217 066 A1

	690	695	700
5	Arg Gly Gln Leu Thr Met Ile Val Gly Gln Val Gly Cys Gly Lys Ser		
	705	710	715 720
	Ser Leu Leu Leu Ala Ala Leu Gly Glu Met Gln Lys Val Ser Gly Ala		
10		725	730 735
	Val Phe Trp Ser Ser Leu Pro Asp Ser Glu Ile Gly Glu Asp Pro Ser		
		740	745 750
15	Pro Glu Arg Glu Thr Ala Thr Asp Leu Asp Ile Arg Lys Arg Gly Pro		
		755	760 765
	Val Ala Tyr Ala Ser Gln Lys Pro Trp Leu Leu Asn Ala Thr Val Glu		
20		770	775 780
	Glu Asn Ile Ile Phe Glu Ser Pro Phe Asn Lys Gln Arg Tyr Lys Met		
		785	790 795 800
25	Val Ile Glu Ala Cys Ser Leu Gln Pro Asp Ile Asp Ile Leu Pro His		
		805	810 815
	Gly Asp Gln Thr Gln Ile Gly Glu Arg Gly Ile Asn Leu Ser Gly Gly		
30		820	825 830
	Gln Arg Gln Arg Ile Ser Val Ala Arg Ala Leu Tyr Gln His Ala Asn		
		835	840 845
35	Val Val Phe Leu Asp Asp Pro Phe Ser Ala Leu Asp Ile His Leu Ser		
		850	855 860
	Asp His Leu Met Gln Ala Gly Ile Leu Glu Leu Leu Arg Asp Asp Lys		
40		865	870 875 880
	Arg Thr Val Val Leu Val Thr His Lys Leu Gln Tyr Leu Pro His Ala		
		885	890 895
45	Asp Trp Ile Ile Ala Met Lys Asp Gly Thr Ile Gln Arg Glu Gly Thr		
		900	905 910
	Leu Lys Asp Phe Gln Arg Ser Glu Cys Gln Leu Phe Glu His Trp Lys		
50		915	920 925
	Thr Leu Met Asn Arg Gln Asp Gln Glu Leu Glu Lys Glu Thr Val Thr		
		930	935 940
55	Glu Arg Lys Ala Thr Glu Pro Pro Gln Gly Leu Ser Arg Ala Met Ser		

EP 1 217 066 A1

	945	950	955	960
5	Ser Arg Asp Gly Leu Leu Gln Asp Glu Glu Glu Glu Glu Glu Ala	965	970	975
10	Ala Glu Ser Glu Glu Asp Asp Asn Leu Ser Ser Met Leu His Gln Arg	980	985	990
	Ala Glu Ile Pro Trp Arg Ala Cys Ala Lys Tyr Leu Ser Ser Ala Gly	995	1000	1005
15	Ile Leu Leu Leu Ser Leu Leu Val Phe Ser Gln Leu Leu Lys His Met	1010	1015	1020
20	Val Leu Val Ala Ile Asp Tyr Trp Leu Ala Lys Trp Thr Asp Ser Ala	1025	1030	1035
	Leu Thr Leu Thr Pro Ala Ala Arg Asn Cys Ser Leu Ser Gln Glu Cys	1045	1050	1055
25	Thr Leu Asp Gln Thr Val Tyr Ala Met Val Phe Thr Val Leu Cys Ser	1060	1065	1070
30	Leu Gly Ile Val Leu Cys Leu Val Thr Ser Val Thr Val Glu Trp Thr	1075	1080	1085
	Gly Leu Lys Val Ala Lys Arg Leu His Arg Ser Leu Leu Asn Arg Ile	1090	1095	1100
35	Ile Leu Ala Pro Met Arg Phe Phe Glu Thr Thr Pro Leu Gly Ser Ile	1105	1110	1115
40	Leu Asn Arg Phe Ser Ser Asp Cys Asn Thr Ile Asp Gln His Ile Pro	1125	1130	1135
	Ser Thr Leu Glu Cys Leu Ser Arg Ser Thr Leu Leu Cys Val Ser Ala	1140	1145	1150
45	Leu Ala Val Ile Ser Tyr Val Thr Pro Val Phe Leu Val Ala Leu Leu	1155	1160	1165
50	Pro Leu Ala Val Val Cys Tyr Phe Ile Gln Lys Tyr Phe Arg Val Ala	1170	1175	1180
55	Ser Arg Asp Leu Gln Gln Leu Asp Asp Thr Thr Gln Leu Pro Leu Leu	1185	1190	1195
	Ser His Phe Ala Glu Thr Val Glu Gly Leu Thr Thr Ile Arg Ala Phe			1200

EP 1 217 066 A1

	1205	1210	1215
5	Arg Tyr Glu Ala Arg Phe Gln Gln Lys Leu Leu Glu Tyr Thr Asp Ser 1220	1225	1230
10	Asn Asn Ile Ala Ser Leu Phe Leu Thr Ala Ala Asn Arg Trp Leu Glu 1235	1240	1245
	Val Arg Met Glu Tyr Ile Gly Ala Cys Val Val Leu Ile Ala Ala Val 1250	1255	1260
15	Thr Ser Ile Ser Asn Ser Leu His Arg Glu Leu Ser Ala Gly Leu Val 1265	1270	1275 1280
20	Gly Leu Gly Leu Thr Tyr Ala Leu Met Val Ser Asn Tyr Leu Asn Trp 1285	1290	1295
	Met Val Arg Asn Leu Ala Asp Met Glu Leu Gln Leu Gly Ala Val Lys 1300	1305	1310
25	Arg Ile His Gly Leu Leu Lys Thr Glu Ala Glu Ser Tyr Glu Gly Leu 1315	1320	1325
30	Leu Ala Pro Ser Leu Ile Pro Lys Asn Trp Pro Asp Gln Gly Lys Ile 1330	1335	1340
	Gln Ile Gln Asn Leu Ser Val Arg Tyr Asp Ser Ser Leu Lys Pro Val 1345	1350	1355 1360
35	Leu Lys His Val Asn Ala Leu Ile Ser Pro Gly Gln Lys Ile Gly Ile 1365	1370	1375
40	Cys Gly Arg Thr Gly Ser Gly Lys Ser Ser Phe Ser Leu Ala Phe Phe 1380	1385	1390
	Arg Met Val Asp Thr Phe Glu Gly His Ile Ile Ile Asp Gly Ile Asp 1395	1400	1405
45	Ile Arg Lys Leu Pro Leu His Thr Leu Pro Ser Arg Leu Ser Ile Ile 1410	1415	1420
50	Leu Gln Asp Pro Val Leu Phe Ser Gly Thr Ile Arg Phe Asn Leu Asp 1425	1430	1435 1440
	Pro Glu Arg Lys Cys Ser Asp Ser Thr Leu Trp Glu Ala Leu Glu Ile 1445	1450	1455
55	Ala Gln Leu Lys Leu Val Val Lys Ala Leu Pro Gly Gly Leu Asp Ala		

EP 1 217 066 A1

	1460	1465	1470
5	Ile Ile Thr Glu Gly Gly Glu Asn Phe Ser Gln Gly Gln Arg Gln Leu 1475	1480	1485
10	Phe Cys Leu Ala Arg Ala Phe Val Arg Lys Thr Ser Ile Phe Ile Met 1490	1495	1500
	Asp Glu Ala Thr Ala Ser Ile Asp Met Ala Thr Glu Asn Ile Leu Gln 1505	1510	1515 1520
15	Lys Val Val Met Thr Ala Phe Ala Asp Arg Thr Val Val Thr Ile Ala 1525	1530	1535
20	His Arg Val His Thr Ile Leu Ser Ala Asp Leu Val Ile Val Leu Lys 1540	1545	1550
	Arg Gly Ala Ile Leu Glu Phe Asp Lys Pro Glu Lys Leu Leu Ser Arg 1555	1560	1565
25	Lys Asp Ser Val Phe Ala Ser Phe Val Arg Ala Asp Lys 1570	1575	1580
30	<210> 68 <211> 1549 <212> PRT <213> Homo sapiens		
35	<400> 68		
40	Met Ser Leu Ser Phe Cys Gly Asn Asn Ile Ser Ser Tyr Asn Ile Asn 1 5 10 15		
	Asp Gly Val Leu Gln Asn Ser Cys Phe Val Asp Ala Leu Asn Leu Val 20 25 30		
45	Pro His Val Phe Leu Leu Phe Ile Thr Phe Pro Ile Leu Phe Ile Gly 35 40 45		
50	Trp Gly Ser Gln Ser Ser Lys Val Gln Ile His His Asn Thr Trp Leu 50 55 60		
	His Phe Pro Gly His Asn Leu Arg Trp Ile Leu Thr Phe Ala Leu Leu 65 70 75 80		
55	Phe Val His Val Cys Glu Ile Ala Glu Gly Ile Val Ser Asp Ser Arg 85 90 95		

EP 1 217 066 A1

	Arg	Glu	Ser	Arg	His	Leu	His	Leu	Phe	Met	Pro	Ala	Val	Met	Gly	Phe	
				100					105					110			
5	Val	Ala	Thr	Thr	Thr	Ser	Ile	Val	Tyr	Tyr	His	Asn	Ile	Glu	Thr	Ser	
			115				120					125					
10	Asn	Phe	Pro	Lys	Leu	Leu	Leu	Ala	Leu	Phe	Leu	Tyr	Trp	Val	Met	Ala	
		130					135					140					
15	Phe	Ile	Thr	Lys	Thr	Ile	Lys	Leu	Val	Lys	Tyr	Cys	Gln	Ser	Gly	Leu	
	145				150					155					160		
	Asp	Ile	Ser	Asn	Leu	Arg	Phe	Cys	Ile	Thr	Gly	Met	Met	Val	Ile	Leu	
				165						170					175		
20	Asn	Gly	Leu	Leu	Met	Ala	Val	Glu	Ile	Asn	Val	Ile	Arg	Val	Arg	Arg	
			180						185				190				
25	Tyr	Val	Phe	Phe	Met	Asn	Pro	Gln	Lys	Val	Lys	Pro	Pro	Glu	Asp	Leu	
		195					200					205					
	Gln	Asp	Leu	Gly	Val	Arg	Phe	Leu	Gln	Pro	Phe	Val	Asn	Leu	Leu	Ser	
		210					215					220					
30	Lys	Ala	Thr	Tyr	Trp	Trp	Met	Asn	Thr	Leu	Ile	Ile	Ser	Ala	His	Lys	
	225				230						235				240		
35	Lys	Pro	Ile	Asp	Leu	Lys	Ala	Ile	Gly	Lys	Leu	Pro	Ile	Ala	Met	Arg	
				245					250					255			
	Ala	Val	Thr	Asn	Tyr	Val	Cys	Leu	Lys	Asp	Ala	Tyr	Glu	Glu	Gln	Lys	
			260					265					270				
40	Lys	Lys	Val	Ala	Asp	His	Pro	Asn	Arg	Thr	Pro	Ser	Ile	Trp	Leu	Ala	
		275					280					285					
45	Met	Tyr	Arg	Ala	Phe	Gly	Arg	Pro	Ile	Leu	Leu	Ser	Ser	Thr	Phe	Arg	
		290					295					300					
50	Tyr	Leu	Ala	Asp	Leu	Leu	Gly	Phe	Ala	Gly	Pro	Leu	Cys	Ile	Ser	Gly	
	305				310					315					320		
	Ile	Val	Gln	Arg	Val	Asn	Glu	Thr	Gln	Asn	Gly	Thr	Asn	Asn	Thr	Thr	
				325					330						335		
55	Gly	Ile	Ser	Glu	Thr	Leu	Ser	Ser	Lys	Glu	Phe	Leu	Glu	Asn	Ala	Tyr	
			340						345				350				

EP 1 217 066 A1

	Val	Leu	Ala	Val	Leu	Leu	Phe	Leu	Ala	Leu	Ile	Leu	Gln	Arg	Thr	Phe	
5																	
	Leu	Gln	Ala	Ser	Tyr	Tyr	Val	Thr	Ile	Glu	Thr	Gly	Ile	Asn	Leu	Arg	
10	Gly	Ala	Leu	Leu	Ala	Met	Ile	Tyr	Asn	Lys	Ile	Leu	Arg	Leu	Ser	Thr	
	Ser	Asn	Leu	Ser	Met	Gly	Glu	Met	Thr	Leu	Gly	Gln	Ile	Asn	Asn	Leu	
15																	
	Val	Ala	Ile	Glu	Thr	Asn	Gln	Leu	Met	Trp	Phe	Leu	Phe	Leu	Cys	Pro	
20	Asn	Leu	Trp	Ala	Met	Pro	Val	Gln	Ile	Ile	Met	Gly	Val	Ile	Leu	Leu	
	Tyr	Asn	Leu	Leu	Gly	Ser	Ser	Ala	Leu	Val	Gly	Ala	Ala	Val	Ile	Val	
25																	
	Leu	Leu	Ala	Pro	Ile	Gln	Tyr	Phe	Ile	Ala	Thr	Lys	Leu	Ala	Glu	Ala	
30	Gln	Lys	Ser	Thr	Leu	Asp	Tyr	Ser	Thr	Glu	Arg	Leu	Lys	Lys	Thr	Asn	
	Glu	Ile	Leu	Lys	Gly	Ile	Lys	Leu	Leu	Lys	Leu	Tyr	Ala	Trp	Glu	His	
35																	
	Ile	Phe	Cys	Lys	Ser	Val	Glu	Glu	Thr	Arg	Met	Lys	Glu	Leu	Ser	Ser	
40	Leu	Lys	Thr	Phe	Ala	Leu	Tyr	Thr	Ser	Leu	Ser	Ile	Phe	Met	Asn	Ala	
	Ala	Ile	Pro	Ile	Ala	Ala	Val	Leu	Ala	Thr	Phe	Val	Thr	His	Ala	Tyr	
45																	
	Ala	Ser	Gly	Asn	Asn	Leu	Lys	Pro	Ala	Glu	Ala	Phe	Ala	Ser	Leu	Ser	
50																	
	Leu	Phe	His	Ile	Leu	Val	Thr	Pro	Leu	Ser	Leu	Leu	Phe	Thr	Val	Val	
55	Arg	Phe	Ala	Val	Lys	Ala	Ile	Ile	Ser	Val	Gln	Lys	Leu	Asn	Glu	Phe	

EP 1 217 066 A1

	Leu	Leu	Ser	Asp	Glu	Ile	Gly	Asp	Asp	Ser	Trp	Arg	Thr	Gly	Glu	Ser	
	610						615					620					
5	Ser	Leu	Pro	Phe	Glu	Ser	Cys	Lys	Lys	His	Thr	Gly	Val	Gln	Pro	Lys	
	625					630					635					640	
10	Thr	Ile	Asn	Arg	Lys	Gln	Pro	Gly	Arg	Tyr	His	Leu	Asp	Ser	Tyr	Glu	
					645					650					655		
	Gln	Ser	Thr	Arg	Arg	Leu	Arg	Pro	Ala	Glu	Thr	Glu	Asp	Ile	Ala	Ile	
15				660				665						670			
	Lys	Val	Thr	Asn	Gly	Tyr	Phe	Ser	Trp	Gly	Ser	Gly	Leu	Ala	Thr	Leu	
		675					680						685				
20	Ser	Asn	Ile	Asp	Ile	Arg	Ile	Pro	Thr	Gly	Gln	Leu	Thr	Met	Ile	Val	
	690					695						700					
	Gly	Gln	Val	Gly	Cys	Gly	Lys	Ser	Ser	Leu	Leu	Leu	Ala	Ile	Leu	Gly	
25	705				710					715						720	
	Glu	Met	Gln	Thr	Leu	Glu	Gly	Lys	Val	His	Trp	Ser	Asn	Val	Asn	Glu	
					725					730						735	
30	Ser	Glu	Pro	Ser	Phe	Glu	Ala	Thr	Arg	Ser	Arg	Asn	Arg	Tyr	Ser	Val	
				740					745					750			
	Ala	Tyr	Ala	Ala	Gln	Lys	Pro	Trp	Leu	Leu	Asn	Ala	Thr	Val	Glu	Glu	
35		755					760						765				
	Asn	Ile	Thr	Phe	Gly	Ser	Pro	Phe	Asn	Lys	Gln	Arg	Tyr	Lys	Ala	Val	
	770					775						780					
40	Thr	Asp	Ala	Cys	Ser	Leu	Gln	Pro	Asp	Ile	Asp	Leu	Leu	Pro	Phe	Gly	
	785					790				795						800	
	Asp	Gln	Thr	Glu	Ile	Gly	Glu	Arg	Gly	Ile	Asn	Leu	Ser	Gly	Gly	Gln	
45				805					810						815		
	Arg	Gln	Arg	Ile	Cys	Val	Ala	Arg	Ala	Leu	Tyr	Gln	Asn	Thr	Asn	Ile	
				820				825						830			
50	Val	Phe	Leu	Asp	Asp	Pro	Phe	Ser	Ala	Leu	Asp	Ile	His	Leu	Ser	Asp	
		835					840						845				
	His	Leu	Met	Gln	Glu	Gly	Ile	Leu	Lys	Phe	Leu	Gln	Asp	Asp	Lys	Arg	
55		850				855						860					

EP 1 217 066 A1

	Thr	Leu	Val	Leu	Val	Thr	His	Lys	Leu	Gln	Tyr	Leu	Thr	His	Ala	Asp	
	865					870					875					880	
5	Trp	Ile	Ile	Ala	Met	Lys	Asp	Gly	Ser	Val	Leu	Arg	Glu	Gly	Thr	Leu	
						885				890					895		
10	Lys	Asp	Ile	Gln	Thr	Lys	Asp	Val	Glu	Leu	Tyr	Glu	His	Trp	Lys	Thr	
						900				905				910			
15	Leu	Met	Asn	Arg	Gln	Asp	Gln	Glu	Leu	Glu	Lys	Asp	Met	Glu	Ala	Asp	
						915				920				925			
20	Gln	Thr	Thr	Leu	Glu	Arg	Lys	Thr	Leu	Arg	Arg	Ala	Met	Tyr	Ser	Arg	
						930				935			940				
25	Glu	Ala	Lys	Ala	Gln	Met	Glu	Asp	Glu	Asp	Glu	Glu	Glu	Glu	Glu	Glu	
						945				950			955			960	
30	Glu	Asp	Glu	Asp	Asp	Asn	Met	Ser	Thr	Val	Met	Arg	Leu	Arg	Thr	Lys	
						965				970				975			
35	Met	Pro	Trp	Lys	Thr	Cys	Trp	Arg	Tyr	Leu	Thr	Ser	Gly	Gly	Phe	Phe	
						980				985				990			
40	Leu	Leu	Ile	Leu	Met	Ile	Phe	Ser	Lys	Leu	Leu	Lys	His	Ser	Val	Ile	
						995				1000				1005			
45	Val	Ala	Ile	Asp	Tyr	Trp	Leu	Ala	Thr	Trp	Thr	Ser	Glu	Tyr	Ser	Ile	
						1010				1015			1020				
50	Asn	Asn	Thr	Gly	Lys	Ala	Asp	Gln	Thr	Tyr	Tyr	Val	Ala	Gly	Phe	Ser	
						1025				1030			1035			1040	
55	Ile	Leu	Cys	Gly	Ala	Gly	Ile	Phe	Leu	Cys	Leu	Val	Thr	Ser	Leu	Thr	
						1045				1050				1055			
60	Val	Glu	Trp	Met	Gly	Leu	Thr	Ala	Ala	Lys	Asn	Leu	His	His	Asn	Leu	
						1060				1065				1070			
65	Leu	Asn	Lys	Ile	Ile	Leu	Gly	Pro	Ile	Arg	Phe	Phe	Asp	Thr	Thr	Pro	
						1075				1080				1085			
70	Leu	Gly	Leu	Ile	Leu	Asn	Arg	Phe	Ser	Ala	Asp	Thr	Asn	Ile	Ile	Asp	
						1090				1095				1100			
75	Gln	His	Ile	Pro	Pro	Thr	Leu	Glu	Ser	Leu	Thr	Arg	Ser	Thr	Leu	Leu	
						1105				1110				1115			1120

EP 1 217 066 A1

	Cys	Leu	Ser	Ala	Ile	Gly	Met	Ile	Ser	Tyr	Ala	Thr	Pro	Val	Phe	Leu	
						1125					1130					1135	
5	Val	Ala	Leu	Leu	Pro	Leu	Gly	Val	Ala	Phe	Tyr	Phe	Ile	Gln	Lys	Tyr	
						1140					1145					1150	
10	Phe	Arg	Val	Ala	Ser	Lys	Asp	Leu	Gln	Glu	Leu	Asp	Asp	Ser	Thr	Gln	
						1155					1160					1165	
15	Leu	Pro	Leu	Leu	Cys	His	Phe	Ser	Glu	Thr	Ala	Glu	Gly	Leu	Thr	Thr	
						1170					1175					1180	
	Ile	Arg	Ala	Phe	Arg	His	Glu	Thr	Arg	Phe	Lys	Gln	Arg	Met	Leu	Glu	
	1185					1190					1195					1200	
20	Leu	Thr	Asp	Thr	Asn	Asn	Ile	Ala	Tyr	Leu	Phe	Leu	Ser	Ala	Ala	Asn	
						1205					1210					1215	
25	Arg	Trp	Leu	Glu	Val	Arg	Thr	Asp	Tyr	Leu	Gly	Ala	Cys	Ile	Val	Leu	
						1220					1225					1230	
	Thr	Ala	Ser	Ile	Ala	Ser	Ile	Ser	Gly	Ser	Ser	Asn	Ser	Gly	Leu	Val	
						1235					1240					1245	
30	Gly	Leu	Gly	Leu	Leu	Tyr	Ala	Leu	Thr	Ile	Thr	Asn	Tyr	Leu	Asn	Trp	
						1250					1255					1260	
35	Val	Val	Arg	Asn	Leu	Ala	Asp	Leu	Glu	Val	Gln	Met	Gly	Ala	Val	Lys	
	1265					1270					1275					1280	
	Lys	Val	Asn	Ser	Phe	Leu	Thr	Met	Glu	Ser	Glu	Asn	Tyr	Glu	Gly	Thr	
						1285					1290					1295	
40	Met	Asp	Pro	Ser	Gln	Val	Pro	Glu	His	Trp	Pro	Gln	Glu	Gly	Glu	Ile	
						1300					1305					1310	
45	Lys	Ile	His	Asp	Leu	Cys	Val	Arg	Tyr	Glu	Asn	Asn	Leu	Lys	Pro	Val	
						1315					1320					1325	
50	Leu	Lys	His	Val	Lys	Ala	Tyr	Ile	Lys	Pro	Gly	Gln	Lys	Val	Gly	Ile	
						1330					1335					1340	
	Cys	Gly	Arg	Thr	Gly	Ser	Gly	Lys	Ser	Ser	Leu	Ser	Leu	Ala	Phe	Phe	
	1345					1350					1355					1360	
55	Arg	Met	Val	Asp	Ile	Phe	Asp	Gly	Lys	Ile	Val	Ile	Asp	Gly	Ile	Asp	
						1365					1370					1375	

EP 1 217 066 A1

Ile Ser Lys Leu Pro Leu His Thr Leu Arg Ser Arg Leu Ser Ile Ile
 1380 1385 1390
 5
 Leu Gln Asp Pro Ile Leu Phe Ser Gly Ser Ile Arg Phe Asn Leu Asp
 1395 1400 1405
 10
 Pro Glu Cys Lys Cys Thr Asp Asp Arg Leu Trp Glu Ala Leu Glu Ile
 1410 1415 1420
 15
 Ala Gln Leu Lys Asn Met Val Lys Ser Leu Pro Gly Gly Leu Asp Ala
 1425 1430 1435 1440
 Val Val Thr Glu Gly Gly Glu Asn Phe Ser Val Gly Gln Arg Gln Leu
 1445 1450 1455
 20
 Phe Cys Leu Ala Arg Ala Phe Val Arg Lys Ser Ser Ile Leu Ile Met
 1460 1465 1470
 25
 Asp Glu Ala Thr Ala Ser Ile Asp Met Ala Thr Glu Asn Ile Leu Gln
 1475 1480 1485
 Lys Val Val Met Thr Ala Phe Ala Asp Arg Thr Val Val Thr Met Ala
 1490 1495 1500
 30
 His Arg Val Ser Ser Ile Met Asp Ala Gly Leu Val Leu Val Phe Ser
 1505 1510 1515 1520
 35
 Glu Gly Ile Leu Val Glu Cys Asp Thr Val Pro Asn Leu Phe Ala His
 1525 1530 1535
 Lys Asn Gly Pro Phe Ser Thr Leu Val Met Thr Asn Lys
 1540 1545
 40
 <210> 69
 <211> 1513
 45
 <212> PRT
 <213> Homo sapiens
 <400> 69
 50
 Gly Ser Gly Cys Leu Gly Ala Glu Lys Arg Glu Gly Lys Asn Arg Trp
 1 5 10 15
 55
 Gln Gly Glu Ala Ser Met Glu Arg Leu Leu Ala Gln Leu Cys Gly Ser
 20 25 30

EP 1 217 066 A1

	Ser	Ala	Ala	Trp	Pro	Leu	Pro	Leu	Trp	Glu	Gly	Asp	Thr	Thr	Gly	His	
5	Cys	Phe	Thr	Gln	Leu	Val	Leu	Ser	Ala	Leu	Pro	His	Ala	Leu	Leu	Ala	
10	Val	Leu	Ser	Ala	Cys	Tyr	Leu	Gly	Thr	Pro	Arg	Ser	Pro	Asp	Tyr	Ile	
	Leu	Pro	Cys	Ser	Pro	Gly	Trp	Arg	Leu	Arg	Leu	Ala	Ala	Ser	Phe	Leu	
15	Leu	Ser	Val	Phe	Pro	Leu	Leu	Asp	Leu	Leu	Pro	Val	Ala	Leu	Pro	Pro	
20	Gly	Ala	Gly	Pro	Gly	Pro	Ile	Gly	Leu	Glu	Val	Leu	Ala	Gly	Cys	Val	
	Ala	Ala	Val	Ala	Trp	Ile	Ser	His	Ser	Leu	Ala	Leu	Trp	Val	Leu	Ala	
25	His	Ser	Pro	His	Gly	His	Ser	Arg	Gly	Pro	Leu	Ala	Leu	Ala	Leu	Val	
30	Ala	Leu	Leu	Pro	Ala	Pro	Ala	Leu	Val	Leu	Thr	Val	Leu	Trp	His	Cys	
	Gln	Arg	Gly	Thr	Leu	Leu	Pro	Pro	Leu	Leu	Pro	Gly	Pro	Met	Ala	Arg	
35	Leu	Cys	Leu	Leu	Ile	Leu	Gln	Leu	Ala	Ala	Leu	Leu	Ala	Tyr	Ala	Leu	
40	Gly	Trp	Ala	Ala	Pro	Gly	Gly	Pro	Arg	Glu	Pro	Trp	Ala	Gln	Glu	Pro	
45	Leu	Leu	Pro	Glu	Asp	Gln	Glu	Pro	Glu	Val	Ala	Glu	Asp	Gly	Glu	Ser	
	Trp	Leu	Ser	Arg	Phe	Ser	Tyr	Ala	Trp	Leu	Ala	Pro	Leu	Leu	Ala	Arg	
50	Gly	Ala	Cys	Gly	Glu	Leu	Arg	Gln	Pro	Gln	Asp	Ile	Cys	Arg	Leu	Pro	
55	His	Arg	Leu	Gln	Pro	Thr	Tyr	Leu	Ala	Arg	Val	Phe	Gln	Ala	His	Trp	

EP 1 217 066 A1

	Gln	Glu	Gly	Ala	Arg	Leu	Trp	Arg	Ala	Leu	Tyr	Gly	Ala	Phe	Gly	Arg	
	290						295					300					
5	Cys	Tyr	Leu	Ala	Leu	Gly	Leu	Leu	Lys	Leu	Val	Gly	Thr	Met	Leu	Gly	
	305					310					315					320	
10	Phe	Ser	Gly	Pro	Leu	Leu	Leu	Ser	Leu	Leu	Val	Gly	Phe	Leu	Glu	Glu	
					325					330					335		
15	Gly	Gln	Glu	Pro	Leu	Ser	His	Gly	Leu	Leu	Tyr	Ala	Leu	Gly	Leu	Ala	
				340				345					350				
20	Gly	Gly	Ala	Val	Leu	Gly	Ala	Val	Leu	Gln	Asn	Gln	Tyr	Gly	Tyr	Glu	
		355					360					365					
25	Val	Tyr	Lys	Val	Thr	Leu	Gln	Ala	Arg	Gly	Ala	Val	Leu	Asn	Ile	Leu	
	370					375						380					
30	Tyr	Cys	Lys	Ala	Leu	Gln	Leu	Gly	Pro	Ser	Arg	Pro	Pro	Thr	Gly	Glu	
	385				390						395					400	
35	Ala	Leu	Asn	Leu	Leu	Gly	Thr	Asp	Ser	Glu	Arg	Leu	Leu	Asn	Phe	Ala	
				405					410						415		
40	Gly	Ser	Phe	His	Glu	Ala	Trp	Gly	Leu	Pro	Leu	Gln	Leu	Ala	Ile	Thr	
				420				425						430			
45	Leu	Tyr	Leu	Leu	Tyr	Gln	Gln	Val	Gly	Val	Ala	Phe	Val	Gly	Gly	Leu	
	435						440						445				
50	Ile	Leu	Ala	Leu	Leu	Leu	Val	Pro	Val	Asn	Lys	Val	Ile	Ala	Thr	Arg	
	450					455						460					
55	Ile	Met	Ala	Ser	Asn	Gln	Glu	Met	Leu	Gln	His	Lys	Asp	Ala	Arg	Val	
	465				470					475						480	
60	Lys	Leu	Val	Thr	Glu	Leu	Leu	Ser	Gly	Ile	Arg	Val	Ile	Lys	Phe	Cys	
				485					490						495		
65	Gly	Trp	Glu	Gln	Ala	Leu	Gly	Ala	Arg	Val	Glu	Ala	Cys	Arg	Ala	Arg	
				500				505						510			
70	Glu	Leu	Gly	Arg	Leu	Arg	Val	Ile	Lys	Tyr	Leu	Asp	Ala	Ala	Cys	Val	
		515					520						525				
75	Tyr	Leu	Trp	Ala	Ala	Leu	Pro	Val	Val	Ile	Ser	Ile	Val	Ile	Phe	Ile	
	530					535						540					

EP 1 217 066 A1

	Thr	Tyr	Val	Leu	Met	Gly	His	Gln	Leu	Thr	Ala	Thr	Lys	Val	Phe	Thr	
	545					550					555					560	
5	Ala	Leu	Ala	Leu	Val	Arg	Met	Leu	Ile	Leu	Pro	Leu	Asn	Asn	Phe	Pro	
					565					570					575		
10	Trp	Val	Ile	Asn	Gly	Leu	Leu	Glu	Ala	Lys	Val	Ser	Leu	Asp	Arg	Ile	
				580					585						590		
	Gln	Leu	Phe	Leu	Asp	Leu	Pro	Asn	His	Asn	Pro	Gln	Ala	Tyr	Tyr	Ser	
15				595				600						605			
	Pro	Asp	Pro	Pro	Ala	Glu	Pro	Ser	Thr	Val	Leu	Glu	Leu	His	Gly	Ala	
		610					615					620					
20	Leu	Phe	Ser	Trp	Asp	Pro	Val	Gly	Thr	Ser	Leu	Glu	Thr	Phe	Ile	Ser	
	625					630					635					640	
	His	Leu	Glu	Val	Lys	Lys	Gly	Met	Leu	Val	Gly	Ile	Val	Gly	Lys	Val	
25					645					650						655	
	Gly	Cys	Gly	Lys	Ser	Ser	Leu	Leu	Ala	Ala	Ile	Ala	Gly	Glu	Leu	His	
				660					665						670		
30	Arg	Leu	Arg	Gly	His	Val	Ala	Val	Arg	Gly	Leu	Ser	Lys	Gly	Phe	Gly	
				675					680						685		
	Leu	Ala	Thr	Gln	Glu	Pro	Trp	Ile	Gln	Phe	Ala	Thr	Ile	Arg	Asp	Asn	
35		690					695						700				
	Ile	Leu	Phe	Gly	Lys	Thr	Phe	Asp	Ala	Gln	Leu	Tyr	Lys	Glu	Val	Leu	
	705					710						715				720	
40	Glu	Ala	Cys	Ala	Leu	Asn	Asp	Asp	Leu	Ser	Ile	Leu	Pro	Ala	Gly	Asp	
					725					730					735		
45	Gln	Thr	Glu	Val	Gly	Glu	Lys	Gly	Val	Thr	Leu	Ser	Gly	Gly	Gln	Arg	
				740					745						750		
	Ala	Arg	Ile	Ala	Leu	Ala	Arg	Ala	Val	Tyr	Gln	Glu	Lys	Glu	Leu	Tyr	
50				755					760						765		
	Leu	Leu	Asp	Asp	Pro	Leu	Ala	Ala	Val	Asp	Ala	Asp	Val	Ala	Asn	His	
			770					775						780			
55	Leu	Leu	His	Arg	Cys	Ile	Leu	Gly	Met	Leu	Ser	Tyr	Thr	Thr	Arg	Leu	
	785					790						795				800	

EP 1 217 066 A1

	Leu Cys Thr His Arg Thr Glu Tyr Leu Glu Arg Ala Asp Ala Val Leu	
	805	810 815
5	Leu Met Glu Ala Gly Arg Leu Ile Arg Ala Gly Pro Pro Ser Glu Ile	
	820	825 830
10	Leu Pro Leu Val Gln Ala Val Pro Lys Ala Trp Ala Glu Asn Gly Gln	
	835	840 845
15	Glu Ser Asp Ser Ala Thr Ala Gln Ser Val Gln Asn Pro Glu Lys Thr	
	850	855 860
	Lys Glu Gly Leu Glu Glu Glu Gln Ser Thr Ser Gly Arg Leu Leu Gln	
	865	870 875 880
20	Glu Glu Ser Lys Lys Glu Gly Ala Val Ala Leu His Val Tyr Gln Ala	
	885	890 895
25	Tyr Trp Lys Ala Val Gly Gln Gly Leu Ala Leu Ala Ile Leu Phe Ser	
	900	905 910
	Leu Leu Leu Met Gln Ala Thr Arg Asn Ala Ala Asp Trp Trp Leu Ser	
	915	920 925
30	His Trp Ile Ser Gln Leu Lys Ala Glu Asn Ser Ser Gln Glu Ala Gln	
	930	935 940
35	Pro Ser Thr Ser Pro Ala Ser Met Gly Leu Phe Ser Pro Gln Leu Leu	
	945	950 955 960
	Leu Phe Ser Pro Gly Asn Leu Tyr Ile Pro Val Phe Pro Leu Pro Lys	
	965	970 975
40	Ala Ala Pro Asn Gly Ser Ser Asp Ile Arg Phe Tyr Leu Thr Val Tyr	
	980	985 990
45	Ala Thr Ile Ala Gly Val Asn Ser Leu Cys Thr Leu Leu Arg Ala Val	
	995	1000 1005
50	Leu Phe Ala Ala Gly Thr Leu Gln Ala Ala Ala Thr Leu His Arg Arg	
	1010	1015 1020
	Leu Leu His Arg Val Leu Met Ala Pro Val Thr Phe Phe Asn Ala Thr	
	1025	1030 1035 1040
55	Pro Thr Gly Arg Ile Leu Asn Arg Phe Ser Ser Asp Val Ala Cys Ala	
	1045	1050 1055

EP 1 217 066 A1

	Asp Asp Ser Leu Pro Phe Ile Leu Asn Ile Leu Leu Ala Asn Ala Ala	
	1060	1065 1070
5	Gly Leu Leu Gly Leu Leu Ala Val Leu Gly Ser Gly Leu Pro Trp Leu	
	1075	1080 1085
10	Leu Leu Leu Leu Pro Pro Leu Ser Ile Met Tyr Tyr His Val Gln Arg	
	1090	1095 1100
	His Tyr Arg Ala Ser Ser Arg Glu Leu Arg Arg Leu Gly Ser Leu Thr	
15	1105	1110 1115 1120
	Leu Ser Pro Leu Tyr Ser His Leu Ala Asp Thr Leu Ala Gly Leu Ser	
	1125	1130 1135
20	Val Leu Arg Ala Thr Gly Ala Thr Tyr Arg Phe Glu Glu Glu Asn Leu	
	1140	1145 1150
	Arg Leu Leu Glu Leu Asn Gln Arg Cys Gln Phe Ala Thr Ser Ala Thr	
25	1155	1160 1165
	Met Gln Trp Leu Asp Ile Arg Leu Gln Leu Met Gly Ala Ala Val Val	
	1170	1175 1180
30	Ser Ala Ile Ala Gly Ile Ala Leu Val Gln His Gln Gln Gly Leu Ala	
	1185	1190 1195 1200
	Asn Pro Gly Leu Val Gly Leu Ser Leu Ser Tyr Ala Leu Ser Leu Thr	
35	1205	1210 1215
	Gly Leu Leu Ser Gly Leu Val Ser Ser Phe Thr Gln Thr Glu Ala Met	
	1220	1225 1230
40	Leu Val Ser Val Glu Arg Leu Glu Glu Tyr Thr Cys Asp Leu Pro Gln	
	1235	1240 1245
	Glu Pro Gln Gly Gln Pro Leu Gln Leu Gly Thr Gly Trp Leu Thr Gln	
45	1250	1255 1260
	Gly Gly Val Glu Phe Gln Asp Val Val Leu Ala Tyr Arg Pro Gly Leu	
50	1265	1270 1275 1280
	Pro Asn Ala Leu Asp Gly Val Thr Phe Cys Val Gln Pro Gly Glu Lys	
	1285	1290 1295
55	Leu Gly Ile Val Gly Arg Thr Gly Ser Gly Lys Ser Ser Leu Leu Leu	
	1300	1305 1310

EP 1 217 066 A1

Val Leu Phe Arg Leu Leu Glu Pro Ser Ser Gly Arg Val Leu Leu Asp
1315 1320 1325

5 Gly Val Asp Thr Ser Gln Leu Glu Leu Ala Gln Leu Arg Ser Gln Leu
1330 1335 1340

Ala Ile Ile Pro Gln Glu Pro Phe Leu Phe Ser Gly Thr Val Arg Glu
10 1345 1350 1355 1360

Asn Leu Asp Pro Gln Gly Leu His Lys Asp Arg Ala Leu Trp Gln Ala
1365 1370 1375

15 Leu Lys Gln Cys His Leu Ser Glu Val Ile Thr Ser Met Gly Gly Leu
1380 1385 1390

Asp Gly Glu Leu Gly Glu Gly Gly Arg Ser Leu Ser Leu Gly Gln Arg
20 1395 1400 1405

Gln Leu Leu Cys Leu Ala Arg Ala Leu Leu Thr Asp Ala Lys Ile Leu
1410 1415 1420

25 Cys Ile Asp Glu Ala Thr Ala Ser Val Asp Gln Lys Thr Asp Gln Leu
1425 1430 1435 1440

Leu Gln Gln Thr Ile Cys Lys Arg Phe Ala Asn Lys Thr Val Leu Thr
30 1445 1450 1455

Ile Ala His Arg Leu Asn Thr Ile Leu Asn Ser Asp Arg Val Leu Val
1460 1465 1470

35 Leu Gln Ala Gly Arg Val Val Glu Leu Asp Ser Pro Ala Thr Leu Arg
1475 1480 1485

40 Asn Gln Pro His Ser Leu Phe Gln Gln Leu Leu Gln Ser Ser Gln Gln
1490 1495 1500

Gly Val Pro Ala Ser Leu Gly Gly Pro
45 1505 1510

<210> 70
50 <211> 745
<212> PRT
<213> Homo sapiens

<400> 70
55 Met Pro Val Leu Ser Arg Pro Arg Pro Trp Arg Gly Asn Thr Leu Lys

EP 1 217 066 A1

	1	5	10	15
5	Arg Thr Ala Val Leu Leu Ala Leu Ala Ala Tyr Gly Ala His Lys Val	20	25	30
	Tyr Pro Leu Val Arg Gln Cys Leu Ala Pro Ala Arg Gly Leu Gln Ala	35	40	45
10	Pro Ala Gly Glu Pro Thr Gln Glu Ala Ser Gly Val Ala Ala Ala Lys	50	55	60
15	Ala Gly Met Asn Arg Val Phe Leu Gln Arg Leu Leu Trp Leu Leu Arg	65	70	75
	Leu Leu Phe Pro Arg Val Leu Cys Arg Glu Thr Gly Leu Leu Ala Leu	85	90	95
20	His Ser Ala Ala Leu Val Ser Arg Thr Phe Leu Ser Val Tyr Val Ala	100	105	110
25	Arg Leu Asp Gly Arg Leu Ala Arg Cys Ile Val Arg Lys Asp Pro Arg	115	120	125
	Ala Phe Gly Trp Gln Leu Leu Gln Trp Leu Leu Ile Ala Leu Pro Ala	130	135	140
30	Thr Phe Val Asn Ser Ala Ile Arg Tyr Leu Glu Gly Gln Leu Ala Leu	145	150	155
	Ser Phe Arg Ser Arg Leu Val Ala His Ala Tyr Arg Leu Tyr Phe Ser	165	170	175
35	Gln Gln Thr Tyr Tyr Arg Val Ser Asn Met Asp Gly Arg Leu Arg Asn	180	185	190
40	Pro Asp Gln Ser Leu Thr Glu Asp Val Val Ala Phe Ala Ala Ser Val	195	200	205
45	Ala His Leu Tyr Ser Asn Leu Thr Lys Pro Leu Leu Asp Val Ala Val	210	215	220
	Thr Ser Tyr Thr Leu Leu Arg Ala Ala Arg Ser Arg Gly Ala Gly Thr	225	230	235
50	Ala Trp Pro Ser Ala Ile Ala Gly Leu Val Val Phe Leu Thr Ala Asn	245	250	255
55	Val Leu Arg Ala Phe Ser Pro Lys Phe Gly Glu Leu Val Ala Glu Glu			

EP 1 217 066 A1

	260	265	270
5	Ala Arg Arg Lys Gly Glu Leu Arg Tyr Met His Ser Arg Val Val Ala 275	280	285
10	Asn Ser Glu Glu Ile Ala Phe Tyr Gly Gly His Glu Val Glu Leu Ala 290	295	300
	Leu Leu Gln Arg Ser Tyr Gln Asp Leu Ala Ser Gln Ile Asn Leu Ile 305	310	315 320
15	Leu Leu Glu Arg Leu Trp Tyr Val Met Leu Glu Gln Phe Leu Met Lys 325	330	335
20	Tyr Val Trp Ser Ala Ser Gly Leu Leu Met Val Ala Val Pro Ile Ile 340	345	350
	Thr Ala Thr Gly Tyr Ser Glu Ser Asp Ala Glu Ala Val Lys Lys Ala 355	360	365
25	Ala Leu Glu Lys Lys Glu Glu Glu Leu Val Ser Glu Arg Thr Glu Ala 370	375	380
30	Phe Thr Ile Ala Arg Asn Leu Leu Thr Ala Ala Ala Asp Ala Ile Glu 385	390	395 400
	Arg Ile Met Ser Ser Tyr Lys Glu Val Thr Glu Leu Ala Gly Tyr Thr 405	410	415
35	Ala Arg Val His Glu Met Phe Gln Val Phe Glu Asp Val Gln Arg Cys 420	425	430
40	His Phe Lys Arg Pro Arg Glu Leu Glu Asp Ala Gln Ala Gly Ser Gly 435	440	445
	Thr Ile Gly Arg Ser Gly Val Arg Val Glu Gly Pro Leu Lys Ile Arg 450	455	460
45	Gly Gln Val Val Asp Val Glu Gln Gly Ile Ile Cys Glu Asn Ile Pro 465	470	475 480
50	Ile Val Thr Pro Ser Gly Glu Val Val Val Ala Ser Leu Asn Ile Arg 485	490	495
	Val Glu Glu Gly Met His Leu Leu Ile Thr Gly Pro Asn Gly Cys Gly 500	505	510
55	Lys Ser Ser Leu Phe Arg Ile Leu Gly Gly Leu Trp Pro Thr Tyr Gly		

EP 1 217 066 A1

	515	520	525
5	Gly Val Leu Tyr Lys Pro Pro Pro Gln Arg Met Phe Tyr Ile Pro Gln 530 535 540		
10	Arg Pro Tyr Met Ser Val Gly Ser Leu Arg Asp Gln Val Ile Tyr Pro 545 550 555 560		
	Asp Ser Val Glu Asp Met Gln Arg Lys Gly Tyr Ser Glu Gln Asp Leu 565 570 575		
15	Glu Ala Ile Leu Asp Val Val His Leu His His Ile Leu Gln Arg Glu 580 585 590		
20	Gly Gly Trp Glu Ala Met Cys Asp Trp Lys Asp Val Leu Ser Gly Gly 595 600 605		
	Glu Lys Gln Arg Ile Gly Met Ala Arg Met Phe Tyr His Arg Pro Lys 610 615 620		
25	Tyr Ala Leu Leu Asp Glu Cys Thr Ser Ala Val Ser Ile Asp Val Glu 625 630 635 640		
30	Gly Lys Ile Phe Gln Ala Ala Lys Asp Ala Gly Ile Ala Leu Leu Ser 645 650 655		
	Ile Thr His Arg Pro Ser Leu Trp Lys Tyr His Thr His Leu Leu Gln 660 665 670		
35	Phe Asp Gly Glu Gly Gly Trp Lys Phe Glu Lys Leu Asp Ser Ala Ala 675 680 685		
40	Arg Leu Ser Leu Thr Glu Glu Lys Gln Arg Leu Glu Gln Gln Leu Ala 690 695 700		
	Gly Ile Pro Lys Met Gln Arg Arg Leu Gln Glu Leu Cys Gln Ile Leu 705 710 715 720		
45	Gly Glu Ala Val Ala Pro Ala His Val Pro Ala Pro Ser Pro Gln Gly 725 730 735		
50	Pro Gly Gly Leu Gln Gly Ala Ser Thr 740 745		
55	<210> 71 <211> 740		

EP 1 217 066 A1

<212> PRT

<213> Homo sapiens

5

<400> 71

Met Thr His Met Leu Asn Ala Ala Ala Asp Arg Val Lys Trp Thr Arg
1 5 10 15

10

Ser Ser Ala Ala Lys Arg Ala Ala Cys Leu Val Ala Ala Ala Tyr Ala
20 25 30

15

Leu Lys Thr Leu Tyr Pro Ile Ile Gly Lys Arg Leu Lys Gln Ser Gly
35 40 45

His Gly Lys Lys Lys Ala Ala Ala Tyr Pro Ala Ala Glu Asn Thr Glu
50 55 60

20

Ile Leu His Cys Thr Glu Thr Ile Cys Glu Lys Pro Ser Pro Gly Val
65 70 75 80

25

Asn Ala Asp Phe Phe Lys Gln Leu Leu Glu Leu Arg Lys Ile Leu Phe
85 90 95

Pro Lys Leu Val Thr Thr Glu Thr Gly Trp Leu Cys Leu His Ser Val
100 105 110

30

Ala Leu Ile Ser Arg Thr Phe Leu Ser Ile Tyr Val Ala Gly Leu Asp
115 120 125

35

Gly Lys Ile Val Lys Ser Ile Val Glu Lys Lys Pro Arg Thr Phe Ile
130 135 140

Ile Lys Leu Ile Lys Trp Leu Met Ile Ala Ile Pro Ala Thr Phe Val
145 150 155 160

40

Asn Ser Ala Ile Arg Tyr Leu Glu Cys Lys Leu Ala Leu Ala Phe Arg
165 170 175

45

Thr Arg Leu Val Asp His Ala Tyr Glu Thr Tyr Phe Thr Asn Gln Thr
180 185 190

Tyr Tyr Lys Val Ile Asn Met Asp Gly Arg Leu Ala Asn Pro Asp Gln
195 200 205

50

Ser Leu Thr Glu Asp Ile Met Met Phe Ser Gln Ser Val Ala His Leu
210 215 220

55

Tyr Ser Asn Leu Thr Lys Pro Ile Leu Asp Val Met Leu Thr Ser Tyr
225 230 235 240

EP 1 217 066 A1

5	Thr Leu Ile Gln Thr Ala Thr Ser Arg Gly Ala Ser Pro Ile Gly Pro	245	250	255
	Thr Leu Leu Ala Gly Leu Val Val Tyr Ala Thr Ala Lys Val Leu Lys	260	265	270
10	Ala Cys Ser Pro Lys Phe Gly Lys Leu Val Ala Glu Glu Ala His Arg	275	280	285
15	Lys Gly Tyr Leu Arg Tyr Val His Ser Arg Ile Ile Ala Asn Val Glu	290	295	300
	Glu Ile Ala Phe Tyr Arg Gly His Lys Val Glu Met Lys Gln Leu Gln	305	310	315
20	Lys Ser Tyr Lys Ala Leu Ala Asp Gln Met Asn Leu Ile Leu Ser Lys	325	330	335
25	Arg Leu Trp Tyr Ile Met Ile Glu Gln Phe Leu Met Lys Tyr Val Trp	340	345	350
	Ser Ser Ser Gly Leu Ile Met Val Ala Ile Pro Ile Ile Thr Ala Thr	355	360	365
30	Gly Phe Ala Asp Gly Glu Asp Gly Gln Lys Gln Val Met Val Ser Glu	370	375	380
35	Arg Thr Glu Ala Phe Thr Thr Ala Arg Asn Leu Leu Ala Ser Gly Ala	385	390	395
	Asp Ala Ile Glu Arg Ile Met Ser Ser Tyr Lys Glu Val Thr Glu Leu	405	410	415
40	Ala Gly Tyr Thr Ala Arg Val Tyr Asn Met Phe Trp Val Phe Asp Glu	420	425	430
45	Val Lys Arg Gly Ile Tyr Lys Arg Thr Ala Val Ile Gln Glu Ser Glu	435	440	445
	Ser His Ser Lys Asn Gly Ala Lys Val Glu Leu Pro Leu Ser Asp Thr	450	455	460
50	Leu Ala Ile Lys Gly Lys Val Ile Asp Val Asp His Gly Ile Ile Cys	465	470	475
	Glu Asn Val Pro Ile Ile Thr Pro Ala Gly Glu Val Val Ala Ser Arg	485	490	495

EP 1 217 066 A1

5	Leu Asn Phe Lys Val Glu Glu Gly Met His Leu Leu Ile Thr Gly Pro	500	505	510
	Asn Gly Cys Gly Lys Ser Ser Leu Phe Arg Ile Leu Ser Gly Leu Trp	515	520	525
10	Pro Val Tyr Glu Gly Val Leu Tyr Lys Pro Pro Pro Gln His Met Phe	530	535	540
	Tyr Ile Pro Gln Arg Pro Tyr Met Ser Leu Gly Ser Leu Arg Asp Gln	545	550	555
15				560
	Val Ile Tyr Pro Asp Ser Val Asp Asp Met His Asp Lys Gly Tyr Thr	565	570	575
20	Asp Gln Asp Leu Glu Arg Ile Leu His Asn Val His Leu Tyr His Ile	580	585	590
	Val Gln Arg Glu Gly Gly Trp Asp Ala Val Met Asp Trp Lys Asp Val	595	600	605
25	Leu Ser Gly Gly Glu Lys Gln Arg Met Gly Met Ala Arg Met Phe Tyr	610	615	620
30	His Lys Pro Lys Tyr Ala Leu Leu Asp Glu Cys Thr Ser Ala Val Ser	625	630	635
				640
35	Ile Asp Val Glu Gly Lys Ile Phe Gln Ala Ala Lys Gly Ala Gly Ile	645	650	655
	Ser Leu Leu Ser Ile Thr His Arg Pro Ser Leu Trp Lys Tyr His Thr	660	665	670
40	His Leu Leu Gln Phe Asp Gly Glu Gly Gly Trp Arg Phe Glu Gln Leu	675	680	685
	Asp Thr Ala Ile Arg Leu Thr Leu Ser Glu Glu Lys Gln Lys Leu Glu	690	695	700
45	Ser Gln Leu Ala Gly Ile Pro Lys Met Gln Gln Arg Leu Asn Glu Leu	705	710	715
50				720
	Cys Lys Ile Leu Gly Glu Asp Ser Val Leu Lys Thr Ile Lys Asn Glu	725	730	735
55	Asp Glu Thr Ser			
		740		

EP 1 217 066 A1

5 <210> 72
 <211> 659
 <212> PRT
 <213> Homo sapiens

10 <400> 72
 Met Ala Ala Phe Ser Lys Tyr Leu Thr Ala Arg Asn Ser Ser Leu Ala
 1 5 10 15

15 Gly Ala Ala Phe Leu Leu Leu Cys Leu Leu His Lys Arg Arg Arg Ala
 20 25 30

20 Leu Gly Leu His Gly Lys Lys Ser Gly Lys Pro Pro Leu Gln Asn Asn
 35 40 45

25 Glu Lys Glu Gly Lys Lys Glu Arg Ala Val Val Asp Lys Val Phe Phe
 50 55 60

30 Ser Arg Leu Ile Gln Ile Leu Lys Ile Met Val Pro Arg Thr Phe Cys
 65 70 75 80

35 Lys Glu Thr Gly Tyr Leu Val Leu Ile Ala Val Met Leu Val Ser Arg
 85 90 95

40 Thr Tyr Cys Asp Val Trp Met Ile Gln Asn Gly Thr Leu Ile Glu Ser
 100 105 110

45 Gly Ile Ile Gly Arg Ser Arg Lys Asp Phe Lys Arg Tyr Leu Leu Asn
 115 120 125

50 Phe Ile Ala Ala Met Pro Leu Ile Ser Leu Val Asn Asn Phe Leu Lys
 130 135 140

55 Tyr Gly Leu Asn Glu Leu Lys Leu Cys Phe Arg Val Arg Leu Thr Lys
 145 150 155 160

60 Tyr Leu Tyr Glu Glu Tyr Leu Gln Ala Phe Thr Tyr Tyr Lys Met Gly
 165 170 175

65 Asn Leu Asp Asn Arg Ile Ala Asn Pro Asp Gln Leu Leu Thr Gln Asp
 180 185 190

70 Val Glu Lys Phe Cys Asn Ser Val Val Asp Leu Tyr Ser Asn Leu Ser
 195 200 205

EP 1 217 066 A1

	Lys	Pro	Phe	Leu	Asp	Ile	Val	Leu	Tyr	Ile	Phe	Lys	Leu	Thr	Ser	Ala	
	210						215					220					
5	Ile	Gly	Ala	Gln	Gly	Pro	Ala	Ser	Met	Met	Ala	Tyr	Leu	Val	Val	Ser	
	225					230					235					240	
10	Gly	Leu	Phe	Leu	Thr	Arg	Leu	Arg	Arg	Pro	Ile	Gly	Lys	Met	Thr	Ile	
					245					250					255		
	Thr	Glu	Gln	Lys	Tyr	Glu	Gly	Glu	Tyr	Arg	Tyr	Val	Asn	Ser	Arg	Leu	
				260					265					270			
15	Ile	Thr	Asn	Ser	Glu	Glu	Ile	Ala	Phe	Tyr	Asn	Gly	Asn	Lys	Arg	Glu	
		275						280					285				
20	Lys	Gln	Thr	Val	His	Ser	Val	Phe	Arg	Lys	Leu	Val	Glu	His	Leu	His	
	290						295					300					
	Asn	Phe	Ile	Leu	Phe	Arg	Phe	Ser	Met	Gly	Phe	Ile	Asp	Ser	Ile	Ile	
25	305					310					315					320	
	Ala	Lys	Tyr	Leu	Ala	Thr	Val	Val	Gly	Tyr	Leu	Val	Val	Ser	Arg	Pro	
				325					330					335			
30	Phe	Leu	Asp	Leu	Ser	His	Pro	Arg	His	Leu	Lys	Ser	Thr	His	Ser	Glu	
		340						345					350				
	Leu	Leu	Glu	Asp	Tyr	Tyr	Gln	Ser	Gly	Arg	Met	Leu	Leu	Arg	Met	Ser	
35		355					360					365					
	Gln	Ala	Leu	Gly	Arg	Ile	Val	Leu	Ala	Gly	Arg	Glu	Met	Thr	Arg	Leu	
	370					375					380						
40	Ala	Gly	Phe	Thr	Ala	Arg	Ile	Thr	Glu	Leu	Met	Gln	Val	Leu	Lys	Asp	
	385					390					395					400	
	Leu	Asn	His	Gly	Lys	Tyr	Glu	Arg	Thr	Met	Val	Ser	Gln	Gln	Glu	Lys	
45				405					410				415				
	Gly	Ile	Glu	Gly	Val	Gln	Val	Ile	Pro	Leu	Ile	Pro	Gly	Ala	Gly	Glu	
		420						425				430					
50	Ile	Ile	Ile	Ala	Asp	Asn	Ile	Ile	Lys	Phe	Asp	His	Val	Pro	Leu	Ala	
		435						440				445					
	Thr	Pro	Asn	Gly	Asp	Val	Leu	Ile	Arg	Asp	Leu	Asn	Phe	Glu	Val	Arg	
55		450					455					460					

EP 1 217 066 A1

Ser Gly Ala Asn Val Leu Ile Cys Gly Pro Asn Gly Cys Gly Lys Ser
 465 470 475 480
 5
 Ser Leu Phe Arg Val Leu Gly Glu Leu Trp Pro Leu Phe Gly Gly Arg
 485 490 495
 10
 Leu Thr Lys Pro Glu Arg Gly Lys Leu Phe Tyr Val Pro Gln Arg Pro
 500 505 510
 Tyr Met Thr Leu Gly Thr Leu Arg Asp Gln Val Ile Tyr Pro Asp Gly
 515 520 525
 15
 Arg Glu Asp Gln Lys Arg Lys Gly Ile Ser Asp Leu Val Leu Lys Glu
 530 535 540
 20
 Tyr Leu Asp Asn Val Gln Leu Gly His Ile Leu Glu Arg Glu Gly Gly
 545 550 555 560
 Trp Asp Ser Val Gln Asp Trp Met Asp Val Leu Ser Gly Gly Glu Lys
 565 570 575
 25
 Gln Arg Met Ala Met Ala Arg Leu Phe Tyr His Lys Pro Gln Phe Ala
 580 585 590
 30
 Ile Leu Asp Glu Cys Thr Ser Ala Val Ser Val Asp Val Glu Gly Tyr
 595 600 605
 Ile Tyr Ser His Cys Arg Lys Val Gly Ile Thr Leu Phe Thr Val Ser
 610 615 620
 35
 His Arg Lys Ser Leu Trp Lys His His Glu Tyr Tyr Leu His Met Asp
 625 630 635 640
 40
 Gly Arg Gly Asn Tyr Glu Phe Lys Gln Ile Thr Glu Asp Thr Val Glu
 645 650 655
 Phe Gly Ser
 45
 <210> 73
 50 <211> 606
 <212> PRT
 <213> Homo sapiens
 55 <400> 73
 Met Ala Val Ala Gly Pro Ala Pro Gly Ala Gly Ala Arg Pro Arg Leu

EP 1 217 066 A1

	1	5	10	15												
5	Asp	Leu	Gln	Phe	Leu	Gln	Arg	Phe	Leu	Gln	Ile	Leu	Lys	Val	Leu	Phe
			20							25					30	
	Pro	Ser	Trp	Ser	Ser	Gln	Asn	Ala	Leu	Met	Phe	Leu	Thr	Leu	Leu	Cys
10			35					40					45			
	Leu	Thr	Leu	Leu	Glu	Gln	Phe	Val	Ile	Tyr	Gln	Val	Gly	Leu	Ile	Pro
		50					55					60				
15	Ser	Gln	Tyr	Tyr	Gly	Val	Leu	Gly	Asn	Lys	Asp	Leu	Glu	Gly	Phe	Lys
	65					70					75				80	
	Thr	Leu	Thr	Phe	Leu	Ala	Val	Met	Leu	Ile	Val	Leu	Asn	Ser	Thr	Leu
20				85						90				95		
	Lys	Ser	Phe	Asp	Gln	Phe	Thr	Cys	Asn	Leu	Leu	Tyr	Val	Ser	Trp	Arg
			100						105				110			
25	Lys	Asp	Leu	Thr	Glu	His	Leu	His	Arg	Leu	Tyr	Phe	Arg	Gly	Arg	Ala
		115					120					125				
	Tyr	Tyr	Thr	Leu	Asn	Val	Leu	Arg	Asp	Asp	Ile	Asp	Asn	Pro	Asp	Gln
30		130				135					140					
	Arg	Ile	Ser	Gln	Asp	Val	Glu	Arg	Phe	Cys	Arg	Gln	Leu	Ser	Ser	Met
	145				150					155			160			
35	Ala	Ser	Lys	Leu	Ile	Ile	Ser	Pro	Phe	Thr	Leu	Val	Tyr	Tyr	Thr	Tyr
			165						170				175			
	Gln	Cys	Phe	Gln	Ser	Thr	Gly	Trp	Leu	Gly	Pro	Val	Ser	Ile	Phe	Gly
40			180					185				190				
	Tyr	Phe	Ile	Leu	Gly	Thr	Val	Val	Asn	Lys	Thr	Leu	Met	Gly	Pro	Ile
		195				200					205					
45	Val	Met	Lys	Leu	Val	His	Gln	Glu	Lys	Leu	Glu	Gly	Asp	Phe	Arg	Phe
	210					215					220					
	Lys	His	Met	Gln	Ile	Arg	Val	Asn	Ala	Glu	Pro	Ala	Ala	Phe	Tyr	Arg
50	225				230					235			240			
	Ala	Gly	His	Val	Glu	His	Met	Arg	Thr	Asp	Arg	Arg	Leu	Gln	Arg	Leu
			245					250				255				
55	Leu	Gln	Thr	Gln	Arg	Glu	Leu	Met	Ser	Lys	Glu	Leu	Trp	Leu	Tyr	Ile

EP 1 217 066 A1

	260	265	270
5	Gly Ile Asn Thr Phe Asp Tyr Leu Gly Ser Ile Leu Ser Tyr Val Val 275	280	285
10	Ile Ala Ile Pro Ile Phe Ser Gly Val Tyr Gly Asp Leu Ser Pro Ala 290	295	300
15	Glu Leu Ser Thr Leu Val Ser Lys Asn Ala Phe Val Cys Ile Tyr Leu 305	310	315 320
20	Ile Ser Cys Phe Thr Gln Leu Ile Asp Leu Ser Thr Thr Leu Ser Asp 325	330	335
25	Val Ala Gly Tyr Thr His Arg Ile Gly Gln Leu Arg Glu Thr Leu Leu 340	345	350
30	Asp Met Ser Leu Lys Ser Gln Asp Cys Glu Ile Leu Gly Glu Ser Glu 355	360	365
35	Trp Gly Leu Asp Thr Pro Pro Gly Trp Pro Ala Ala Glu Pro Ala Asp 370	375	380
40	Thr Ala Phe Leu Leu Glu Arg Val Ser Ile Ser Ala Pro Ser Ser Asp 385	390	395 400
45	Lys Pro Leu Ile Lys Asp Leu Ser Leu Lys Ile Ser Glu Gly Gln Ser 405	410	415
50	Leu Leu Ile Thr Gly Asn Thr Gly Thr Gly Lys Thr Ser Leu Leu Arg 420	425	430
55	Val Leu Gly Gly Leu Trp Thr Ser Thr Arg Gly Ser Val Gln Met Leu 435	440	445
60	Thr Asp Phe Gly Pro His Gly Val Leu Phe Leu Pro Gln Lys Pro Phe 450	455	460
65	Phe Thr Asp Gly Thr Leu Arg Glu Gln Val Ile Tyr Pro Leu Lys Glu 465	470	475 480
70	Val Tyr Pro Asp Ser Gly Ser Ala Asp Asp Glu Arg Ile Leu Arg Phe 485	490	495
75	Leu Glu Leu Ala Gly Leu Ser Asn Leu Val Ala Arg Thr Glu Gly Leu 500	505	510
80	Asp Gln Gln Val Asp Trp Asn Trp Tyr Asp Val Leu Ser Pro Gly Glu		

EP 1 217 066 A1

	515	520	525
5	Met Gln Arg Leu Ser Phe Ala Arg Leu Phe Tyr Leu Gln Pro Lys Tyr		
	530	535	540
10	Ala Val Leu Asp Glu Ala Thr Ser Ala Leu Thr Glu Glu Val Glu Ser		
	545	550	555 560
	Glu Leu Tyr Arg Ile Gly Gln Gln Leu Gly Met Thr Phe Ile Ser Val		
	565	570	575
15	Gly His Arg Gln Ser Leu Glu Lys Phe His Ser Leu Val Leu Lys Leu		
	580	585	590
20	Cys Gly Gly Gly Arg Trp Glu Leu Met Arg Ile Lys Val Glu		
	595	600	605
25	<210> 74		
	<211> 599		
	<212> PRT		
	<213> Homo sapiens		
30	<400> 74		
	Met Ala Asp Lys Leu Thr Arg Ile Ala Ile Val Asn His Asp Lys Cys		
	1 5 10 15		
35	Lys Pro Lys Lys Cys Arg Gln Glu Cys Lys Lys Ser Cys Pro Val Val		
	20 25 30		
40	Arg Met Gly Lys Leu Cys Ile Glu Val Thr Pro Gln Ser Lys Ile Ala		
	35 40 45		
	Trp Ile Ser Glu Thr Leu Cys Ile Gly Cys Gly Ile Cys Ile Lys Lys		
	50 55 60		
45	Cys Pro Phe Gly Ala Leu Ser Ile Val Asn Leu Pro Ser Asn Leu Glu		
	65 70 75 80		
50	Lys Glu Thr Thr His Arg Tyr Cys Ala Asn Ala Phe Lys Leu His Arg		
	85 90 95		
	Leu Pro Ile Pro Arg Pro Gly Glu Val Leu Gly Leu Val Gly Thr Asn		
	100 105 110		
55	Gly Ile Gly Lys Ser Ala Ala Leu Lys Ile Leu Ala Gly Lys Gln Lys		
	115 120 125		

EP 1 217 066 A1

	Pro	Asn	Leu	Gly	Lys	Tyr	Asp	Asp	Pro	Pro	Asp	Trp	Gln	Glu	Ile	Leu	
5			130						135					140			
	Thr	Tyr	Phe	Arg	Gly	Ser	Glu	Leu	Gln	Asn	Tyr	Phe	Thr	Lys	Ile	Leu	
	145					150					155					160	
10																	
	Glu	Asp	Asp	Leu	Lys	Ala	Ile	Ile	Lys	Pro	Gln	Tyr	Val	Ala	Arg	Phe	
					165					170						175	
15	Leu	Arg	Leu	Ala	Lys	Gly	Thr	Val	Gly	Ser	Ile	Leu	Asp	Arg	Lys	Asp	
				180					185						190		
	Glu	Thr	Lys	Thr	Gln	Ala	Ile	Val	Cys	Gln	Gln	Leu	Asp	Leu	Thr	His	
			195					200						205			
20																	
	Leu	Lys	Glu	Arg	Asn	Val	Glu	Asp	Leu	Ser	Gly	Gly	Glu	Leu	Gln	Arg	
		210					215					220					
25	Phe	Ala	Cys	Ala	Val	Val	Cys	Ile	Gln	Lys	Ala	Asp	Ile	Phe	Met	Phe	
	225					230					235					240	
	Asp	Glu	Pro	Ser	Ser	Tyr	Leu	Asp	Val	Lys	Gln	Arg	Leu	Lys	Ala	Ala	
					245					250					255		
30																	
	Ile	Thr	Ile	Arg	Ser	Leu	Ile	Asn	Pro	Asp	Arg	Tyr	Ile	Ile	Val	Val	
				260					265					270			
35	Glu	His	Asp	Leu	Ser	Val	Leu	Asp	Tyr	Leu	Ser	Asp	Phe	Ile	Cys	Cys	
			275					280					285				
	Leu	Tyr	Gly	Val	Pro	Ser	Ala	Tyr	Gly	Val	Val	Thr	Met	Pro	Phe	Ser	
		290					295					300					
40																	
	Val	Arg	Glu	Gly	Ile	Asn	Ile	Phe	Leu	Asp	Gly	Tyr	Val	Pro	Thr	Glu	
	305					310					315					320	
45	Asn	Leu	Arg	Phe	Arg	Asp	Ala	Ser	Leu	Val	Phe	Lys	Val	Ala	Glu	Thr	
					325					330					335		
	Ala	Asn	Glu	Glu	Glu	Val	Lys	Lys	Met	Cys	Met	Tyr	Lys	Tyr	Pro	Gly	
					340				345					350			
50																	
	Met	Lys	Lys	Lys	Met	Gly	Glu	Phe	Glu	Leu	Ala	Ile	Val	Ala	Gly	Glu	
			355					360									

EP 1 217 066 A1

5 Lys Thr Thr Phe Ile Arg Met Leu Ala Gly Arg Leu Lys Pro Asp Glu
 385 390 395 400
 Gly Gly Glu Val Pro Val Leu Asn Val Ser Tyr Lys Pro Gln Lys Ile
 405 410 415
 10 Ser Pro Lys Ser Thr Gly Ser Val Arg Gln Leu Leu His Glu Lys Ile
 420 425 430
 Arg Asp Ala Tyr Thr His Pro Gln Phe Val Thr Asp Val Met Lys Pro
 15 435 440 445
 Leu Gln Ile Glu Asn Ile Ile Asp Gln Glu Val Gln Thr Leu Ser Gly
 450 455 460
 20 Gly Glu Leu Gln Arg Val Arg Leu Arg Leu Cys Leu Gly Lys Pro Ala
 465 470 475 480
 Asp Val Tyr Leu Ile Asp Glu Pro Ser Ala Tyr Leu Asp Ser Glu Gln
 25 485 490 495
 Arg Leu Met Ala Ala Arg Val Val Lys Arg Phe Ile Leu His Ala Lys
 500 505 510
 30 Lys Thr Ala Phe Val Val Glu His Asp Phe Ile Met Ala Thr Tyr Leu
 515 520 525
 Ala Asp Arg Val Ile Val Phe Asp Gly Val Pro Ser Lys Asn Thr Val
 35 530 535 540
 Ala Asn Ser Pro Gln Thr Leu Leu Ala Gly Met Asn Lys Phe Leu Ser
 545 550 555 560
 40 Gln Leu Glu Ile Thr Phe Arg Arg Asp Pro Asn Asn Tyr Arg Pro Arg
 565 570 575
 Ile Asn Lys Leu Asn Ser Ile Lys Asp Val Glu Gln Lys Lys Ser Gly
 45 580 585 590
 Asn Tyr Phe Phe Leu Asp Asp
 595
 50
 <210> 75
 <211> 807
 55 <212> PRT

EP 1 217 066 A1

<213> Homo sapiens

<400> 75

5	Met	Pro	Lys	Ala	Pro	Lys	Gln	Gln	Pro	Pro	Glu	Pro	Glu	Trp	Ile	Gly	
	1				5					10					15		
10	Asp	Gly	Glu	Ser	Thr	Ser	Pro	Ser	Asp	Lys	Val	Val	Lys	Lys	Gly	Lys	
				20					25					30			
	Lys	Asp	Lys	Lys	Ile	Lys	Lys	Thr	Phe	Phe	Glu	Glu	Leu	Ala	Val	Glu	
			35					40						45			
15	Asp	Lys	Gln	Ala	Gly	Glu	Glu	Glu	Lys	Val	Leu	Lys	Glu	Lys	Glu	Gln	
		50						55					60				
20	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Lys	Lys	Lys	Arg	Asp	Thr	Arg	
	65						70					75				80	
	Lys	Gly	Arg	Arg	Lys	Lys	Asp	Val	Asp	Asp	Asp	Gly	Glu	Glu	Lys	Glu	
					85					90					95		
25	Leu	Met	Glu	Arg	Leu	Lys	Lys	Leu	Ser	Val	Pro	Thr	Ser	Asp	Glu	Glu	
				100					105					110			
30	Asp	Glu	Val	Pro	Ala	Pro	Lys	Pro	Arg	Gly	Gly	Lys	Lys	Thr	Lys	Gly	
			115					120					125				
	Gly	Asn	Val	Phe	Ala	Ala	Leu	Ile	Gln	Asp	Gln	Ser	Glu	Glu	Glu	Glu	
		130					135					140					
35	Glu	Glu	Glu	Lys	His	Pro	Pro	Lys	Pro	Ala	Lys	Pro	Glu	Lys	Asn	Arg	
	145					150					155				160		
40	Ile	Asn	Lys	Ala	Val	Ser	Glu	Glu	Gln	Gln	Pro	Ala	Leu	Lys	Gly	Lys	
				165						170					175		
	Lys	Gly	Lys	Glu	Glu	Lys	Ser	Lys	Gly	Lys	Ala	Lys	Pro	Gln	Asn	Lys	
			180						185					190			
45	Phe	Ala	Ala	Leu	Asp	Asn	Glu	Glu	Glu	Asp	Lys	Glu	Glu	Glu	Ile	Ile	
		195						200					205				
50	Lys	Glu	Lys	Glu	Pro	Pro	Lys	Gln	Gly	Lys	Glu	Lys	Ala	Lys	Lys	Ala	
		210					215					220					
	Glu	Gln	Met	Glu	Tyr	Glu	Arg	Gln	Val	Ala	Ser	Leu	Lys	Ala	Ala	Asn	
55	225					230					235				240		

EP 1 217 066 A1

	Ala	Ala	Glu	Asn	Asp	Phe	Ser	Val	Ser	Gln	Ala	Glu	Met	Ser	Ser	Arg	
5	Gln	Ala	Met	Leu	Glu	Asn	Ala	Ser	Asp	Ile	Lys	Leu	Glu	Lys	Phe	Ser	
10	Ile	Ser	Ala	His	Gly	Lys	Glu	Leu	Phe	Val	Asn	Ala	Asp	Leu	Tyr	Ile	
	Val	Ala	Gly	Arg	Arg	Tyr	Gly	Leu	Val	Gly	Pro	Asn	Gly	Lys	Gly	Lys	
15	Thr	Thr	Leu	Leu	Lys	His	Ile	Ala	Asn	Arg	Ala	Leu	Ser	Ile	Pro	Pro	
20	Asn	Ile	Asp	Val	Leu	Leu	Cys	Glu	Gln	Glu	Val	Val	Ala	Asp	Glu	Thr	
	Pro	Ala	Val	Gln	Ala	Val	Leu	Arg	Ala	Asp	Thr	Lys	Arg	Leu	Lys	Leu	
25	Leu	Glu	Glu	Glu	Arg	Arg	Leu	Gln	Gly	Gln	Leu	Glu	Gln	Gly	Asp	Asp	
30	Thr	Ala	Ala	Glu	Arg	Leu	Glu	Lys	Val	Tyr	Glu	Glu	Leu	Arg	Ala	Thr	
	Gly	Ala	Ala	Ala	Ala	Glu	Ala	Lys	Ala	Arg	Arg	Ile	Leu	Ala	Gly	Leu	
35	Gly	Phe	Asp	Pro	Glu	Met	Gln	Asn	Arg	Pro	Thr	Gln	Lys	Phe	Ser	Gly	
40	Gly	Trp	Arg	Met	Arg	Val	Ser	Leu	Ala	Arg	Ala	Leu	Phe	Met	Glu	Pro	
	Thr	Leu	Leu	Met	Leu	Asp	Glu	Pro	Thr	Asn	His	Leu	Asp	Leu	Asn	Ala	
45	Val	Ile	Trp	Leu	Asn	Asn	Tyr	Leu	Gln	Gly	Trp	Arg	Lys	Thr	Leu	Leu	
50	Ile	Val	Ser	His	Asp	Gln	Gly	Phe	Leu	Asp	Asp	Val	Cys	Thr	Asp	Ile	
	Ile	His	Leu	Asp	Ala	Gln	Arg	Leu	His	Tyr	Tyr	Arg	Gly	Asn	Tyr	Met	
55																	

EP 1 217 066 A1

	Thr Phe Lys Lys Met Tyr Gln Gln Lys Gln Lys Glu Leu Leu Lys Gln	
	500	510
5	Tyr Glu Lys Gln Glu Lys Lys Leu Lys Glu Leu Lys Ala Gly Gly Lys	
	515	525
10	Ser Thr Lys Gln Ala Glu Lys Gln Thr Lys Glu Ala Leu Thr Arg Lys	
	530	540
	Gln Gln Lys Cys Arg Arg Lys Asn Gln Asp Glu Glu Ser Gln Glu Ala	
	545	560
15	Pro Glu Leu Leu Lys Arg Pro Lys Glu Tyr Thr Val Arg Phe Thr Phe	
	565	575
20	Pro Asp Pro Pro Pro Leu Ser Pro Pro Val Leu Gly Leu His Gly Val	
	580	590
	Thr Phe Gly Tyr Gln Gly Gln Lys Pro Leu Phe Lys Asn Leu Asp Phe	
	595	605
25	Gly Ile Asp Met Asp Ser Arg Ile Cys Ile Val Gly Pro Asn Gly Val	
	610	620
30	Gly Lys Ser Thr Leu Leu Leu Leu Thr Gly Lys Leu Thr Pro Thr	
	625	640
	His Gly Glu Met Arg Lys Asn His Arg Leu Lys Ile Gly Phe Phe Asn	
	645	655
35	Gln Gln Tyr Ala Glu Gln Leu Arg Met Glu Glu Thr Pro Thr Glu Tyr	
	660	670
40	Leu Gln Arg Gly Phe Asn Leu Pro Tyr Gln Asp Ala Arg Lys Cys Leu	
	675	685
	Gly Arg Phe Gly Leu Glu Ser His Ala His Thr Ile Gln Ile Cys Lys	
	690	700
45	Leu Ser Gly Gly Gln Lys Ala Arg Val Val Phe Ala Glu Leu Ala Cys	
	705	720
50	Arg Glu Pro Asp Val Leu Ile Leu Asp Glu Pro Thr Asn Asn Leu Asp	
	725	735
	Ile Glu Ser Ile Asp Ala Leu Gly Glu Ala Ile Asn Glu Tyr Lys Gly	
	740	750
55		

EP 1 217 066 A1

Ala Val Ile Val Val Ser His Asp Ala Arg Leu Ile Thr Glu Thr Asn
755 760 765

5

Cys Gln Leu Trp Val Val Glu Glu Gln Ser Val Ser Gln Ile Asp Gly
770 775 780

10

Asp Phe Glu Asp Tyr Lys Arg Glu Val Leu Glu Ala Leu Gly Glu Val
785 790 795 800

Met Val Ser Arg Pro Arg Glu
805

15

<210> 76
<211> 634
<212> PRT
<213> Homo sapiens

20

<400> 76
Met Pro Ser Asp Leu Ala Lys Lys Lys Ala Ala Lys Lys Lys Glu Ala
1 5 10 15

25

Ala Lys Ala Arg Gln Arg Pro Arg Lys Gly His Glu Glu Asn Gly Asp
20 25 30

30

Val Val Thr Glu Pro Gln Val Ala Glu Lys Asn Glu Ala Asn Gly Arg
35 40 45

35

Glu Thr Thr Glu Val Asp Leu Leu Thr Lys Glu Leu Glu Asp Phe Glu
50 55 60

40

Met Lys Lys Ala Ala Ala Arg Ala Val Thr Gly Val Leu Ala Ser His
65 70 75 80

Pro Asn Ser Thr Asp Val His Ile Ile Asn Leu Ser Leu Thr Phe His
85 90 95

45

Gly Gln Glu Leu Leu Ser Asp Thr Lys Leu Glu Leu Asn Ser Gly Arg
100 105 110

Arg Tyr Gly Leu Ile Gly Leu Asn Gly Ile Gly Lys Ser Met Leu Leu
115 120 125

50

Ser Ala Ile Gly Lys Arg Glu Val Pro Ile Pro Glu His Ile Asp Ile
130 135 140

55

Tyr His Leu Thr Arg Glu Met Pro Pro Ser Asp Lys Thr Pro Leu His

EP 1 217 066 A1

	145		150		155		160
5	Cys Val Met Glu Val Asp Thr Glu Arg Ala Met Leu Glu Lys Glu Ala	165		170		175	
	Glu Arg Leu Ala His Glu Asp Ala Glu Cys Glu Lys Leu Met Glu Leu	180		185		190	
10	Tyr Glu Arg Leu Glu Glu Leu Asp Ala Asp Lys Ala Glu Met Arg Ala	195		200		205	
	Ser Arg Ile Leu His Gly Leu Gly Phe Thr Pro Ala Met Gln Arg Lys	210		215		220	
	Lys Leu Lys Asp Phe Ser Gly Gly Trp Arg Met Arg Val Ala Leu Ala	225		230		235	240
20	Arg Ala Leu Phe Ile Arg Pro Phe Met Leu Leu Leu Asp Glu Pro Thr	245		250		255	
	Asn His Leu Asp Leu Asp Ala Cys Val Trp Leu Glu Glu Glu Leu Lys	260		265		270	
	Thr Phe Lys Arg Ile Leu Val Leu Val Ser His Ser Gln Asp Phe Leu	275		280		285	
30	Asn Gly Val Cys Thr Asn Ile Ile His Met His Asn Lys Lys Leu Lys	290		295		300	
	Tyr Tyr Thr Gly Asn Tyr Asp Gln Tyr Val Lys Thr Arg Leu Glu Leu	305		310		315	320
	Glu Glu Asn Gln Met Lys Arg Phe His Trp Glu Gln Asp Gln Ile Ala	325		330		335	
40	His Met Lys Asn Tyr Ile Ala Arg Phe Gly His Gly Ser Ala Lys Leu	340		345		350	
	Ala Arg Gln Ala Gln Ser Lys Glu Lys Thr Leu Gln Lys Met Met Ala	355		360		365	
	Ser Gly Leu Thr Glu Arg Val Val Ser Asp Lys Thr Leu Ser Phe Tyr	370		375		380	
50	Phe Pro Pro Cys Gly Lys Ile Pro Pro Pro Val Ile Met Val Gln Asn	385		390		395	400
	Val Ser Phe Lys Tyr Thr Lys Asp Gly Pro Cys Ile Tyr Asn Asn Leu						
55							

EP 1 217 066 A1

	405	410	415
5	Glu Phe Gly Ile Asp Leu Asp Thr Arg Val Ala Leu Val Gly Pro Asn 420	425	430
10	Gly Ala Gly Lys Ser Thr Leu Leu Lys Leu Leu Thr Gly Glu Leu Leu 435	440	445
	Pro Thr Asp Gly Met Ile Arg Lys His Ser His Val Lys Ile Gly Arg 450	455	460
15	Tyr His Gln His Leu Gln Glu Gln Leu Asp Leu Asp Leu Ser Pro Leu 465	470	475 480
20	Glu Tyr Met Met Lys Cys Tyr Pro Glu Ile Lys Glu Lys Glu Glu Met 485	490	495
	Arg Lys Ile Ile Gly Arg Tyr Gly Leu Thr Gly Lys Gln Gln Val Ser 500	505	510
25	Pro Ile Arg Asn Leu Ser Asp Gly Gln Lys Cys Arg Val Cys Leu Ala 515	520	525
30	Trp Leu Ala Trp Gln Asn Pro His Met Leu Phe Leu Asp Glu Pro Thr 530	535	540
	Asn His Leu Asp Ile Glu Thr Ile Asp Ala Leu Ala Asp Ala Ile Asn 545	550	555 560
35	Glu Phe Glu Gly Gly Met Met Leu Val Ser His Asp Phe Arg Leu Ile 565	570	575
40	Gln Gln Val Ala Gln Glu Ile Trp Val Cys Glu Lys Gln Thr Ile Thr 580	585	590
	Lys Trp Pro Gly Asp Ile Leu Ala Tyr Lys Glu His Leu Lys Ser Lys 595	600	605
45	Leu Val Asp Glu Glu Pro Gln Leu Thr Lys Arg Thr His Asn Val Cys 610	615	620
50	Thr Leu Thr Leu Ala Ser Leu Pro Arg Pro 625	630	
55	<210> 77 <211> 709		

EP 1 217 066 A1

<212> PRT

<213> Homo sapiens

5

<400> 77

Met Ala Thr Cys Ala Glu Ile Leu Arg Ser Glu Phe Pro Glu Ile Asp
1 5 10 15

10

Gly Gln Val Phe Asp Tyr Val Thr Gly Val Leu His Ser Gly Ser Ala
20 25 30

15

Asp Phe Glu Ser Val Asp Asp Leu Val Glu Ala Val Gly Glu Leu Leu
35 40 45

Gln Glu Val Ser Gly Asp Ser Lys Asp Asp Ala Gly Ile Arg Ala Val
50 55 60

20

Cys Gln Arg Met Tyr Asn Thr Leu Arg Leu Ala Glu Pro Gln Ser Gln
65 70 75 80

25

Gly Asn Ser Gln Val Leu Leu Asp Ala Pro Ile Gln Leu Ser Lys Ile
85 90 95

Thr Glu Asn Tyr Asp Cys Gly Thr Lys Leu Pro Gly Leu Leu Lys Arg
100 105 110

30

Glu Gln Ser Ser Thr Val Asn Ala Lys Lys Leu Glu Lys Ala Glu Ala
115 120 125

35

Arg Leu Lys Ala Lys Gln Glu Lys Arg Ser Glu Lys Asp Thr Leu Lys
130 135 140

Thr Ser Asn Pro Leu Val Leu Glu Glu Ala Ser Ala Ser Gln Ala Gly
145 150 155 160

40

Ser Arg Lys Glu Ser Arg Leu Glu Ser Ser Gly Lys Asn Lys Ser Tyr
165 170 175

45

Asp Val Arg Ile Glu Asn Phe Asp Val Ser Phe Gly Asp Arg Val Leu
180 185 190

Leu Ala Gly Ala Asp Val Asn Leu Ala Trp Gly Arg Arg Tyr Gly Leu
195 200 205

50

Val Gly Arg Asn Gly Leu Gly Lys Thr Thr Leu Leu Lys Met Leu Ala
210 215 220

55

Thr Arg Ser Leu Arg Val Pro Ala His Ile Ser Leu Leu His Val Glu
225 230 235 240

EP 1 217 066 A1

5	Gln Glu Val Ala Gly Asp Asp Thr Pro Ala Leu Gln Ser Val Leu Glu	245	250	255
	Ser Asp Ser Val Arg Glu Asp Leu Leu Arg Arg Glu Arg Glu Leu Thr	260	265	270
10	Ala Gln Ile Ala Ala Gly Arg Ala Glu Gly Ser Glu Ala Ala Glu Leu	275	280	285
15	Ala Glu Ile Tyr Ala Lys Leu Glu Glu Ile Glu Ala Asp Lys Ala Pro	290	295	300
	Ala Arg Ala Ser Val Ile Leu Ala Gly Leu Gly Phe Thr Pro Lys Met	305	310	315
20	Gln Gln Gln Pro Thr Arg Glu Phe Ser Gly Gly Trp Arg Met Arg Leu	325	330	335
25	Ala Leu Ala Arg Ala Leu Phe Ala Arg Pro Asp Leu Leu Leu Leu Asp	340	345	350
	Glu Pro Thr Asn Met Leu Asp Val Arg Ala Ile Leu Trp Leu Glu Asn	355	360	365
30	Tyr Leu Gln Thr Trp Pro Ser Thr Ile Leu Val Val Ser His Asp Arg	370	375	380
35	Asn Phe Leu Asn Ala Ile Ala Thr Asp Ile Ile His Leu His Ser Gln	385	390	395
	Arg Leu Asp Gly Tyr Arg Gly Asp Phe Glu Thr Phe Ile Lys Ser Lys	405	410	415
40	Gln Glu Arg Leu Leu Asn Gln Gln Arg Glu Tyr Glu Ala Gln Gln Gln	420	425	430
45	Tyr Arg Gln His Ile Gln Val Phe Ile Asp Arg Phe Arg Tyr Asn Ala	435	440	445
	Asn Arg Ala Ser Gln Val Gln Ser Lys Leu Lys Met Leu Glu Lys Leu	450	455	460
50	Pro Glu Leu Arg Pro Val Asp Lys Glu Ser Glu Val Val Met Lys Phe	465	470	475
55	Pro Asp Gly Phe Glu Lys Phe Ser Pro Pro Ile Leu Gln Leu Asp Glu	485	490	495

EP 1 217 066 A1

5	Val Asp Phe Tyr Tyr Asp Pro Lys His Val Ile Phe Ser Arg Leu Ser	500	505	510
	Val Ser Ala Asp Leu Glu Ser Arg Ile Cys Val Val Gly Glu Asn Gly	515	520	525
10	Ala Gly Lys Ser Thr Met Leu Lys Leu Leu Leu Gly Asp Leu Ala Pro	530	535	540
15	Val Arg Gly Ile Arg His Ala His Arg Asn Leu Lys Ile Gly Tyr Phe	545	550	555
	Ser Gln His His Val Glu Gln Leu Asp Leu Asn Val Ser Ala Val Glu	565	570	575
20	Leu Leu Ala Arg Lys Phe Pro Gly Arg Pro Glu Glu Glu Tyr Arg His	580	585	590
25	Gln Leu Gly Arg Tyr Gly Ile Ser Gly Glu Leu Ala Met Arg Pro Leu	595	600	605
	Ala Ser Leu Ser Gly Gly Gln Lys Ser Arg Val Ala Phe Ala Gln Met	610	615	620
30	Thr Met Pro Cys Pro Asn Phe Tyr Ile Leu Asp Glu Pro Thr Asn His	625	630	635
35	Leu Asp Met Glu Thr Ile Glu Ala Leu Gly Arg Ala Leu Asn Asn Phe	645	650	655
	Arg Gly Gly Val Ile Leu Val Ser His Asp Glu Arg Phe Ile Arg Leu	660	665	670
40	Val Cys Arg Glu Leu Trp Val Cys Glu Gly Gly Gly Val Thr Arg Val	675	680	685
45	Glu Gly Gly Phe Asp Gln Tyr Arg Ala Leu Leu Gln Glu Gln Phe Arg	690	695	700
50	Arg Glu Gly Phe Leu	705		
55	<210> 78			
	<211> 674			
	<212> PRT			

EP 1 217 066 A1

<213> Homo sapiens

<400> 78

5	Met	Ala	Ala	Phe	Ser	Val	Gly	Thr	Ala	Met	Asn	Ala	Ser	Ser	Tyr	Ser
	1				5					10					15	
10	Ala	Glu	Met	Thr	Glu	Pro	Lys	Ser	Val	Cys	Val	Ser	Val	Asp	Glu	Val
				20				25						30		
15	Val	Ser	Ser	Asn	Met	Glu	Ala	Thr	Glu	Thr	Asp	Leu	Leu	Asn	Gly	His
			35					40					45			
20	Leu	Lys	Lys	Val	Asp	Asn	Asn	Leu	Thr	Glu	Ala	Gln	Arg	Phe	Ser	Ser
	50					55						60				
25	Leu	Pro	Arg	Arg	Ala	Ala	Val	Asn	Ile	Glu	Phe	Arg	Asp	Leu	Ser	Tyr
	65				70					75					80	
30	Ser	Val	Pro	Glu	Gly	Pro	Trp	Trp	Arg	Lys	Lys	Gly	Tyr	Lys	Thr	Leu
				85					90						95	
35	Leu	Lys	Gly	Ile	Ser	Gly	Lys	Phe	Asn	Ser	Gly	Glu	Leu	Val	Ala	Ile
			100					105					110			
40	Met	Gly	Pro	Ser	Gly	Ala	Gly	Lys	Ser	Thr	Leu	Met	Asn	Ile	Leu	Ala
		115						120					125			
45	Gly	Tyr	Arg	Glu	Thr	Gly	Met	Lys	Gly	Ala	Val	Leu	Ile	Asn	Gly	Leu
		130					135					140				
50	Pro	Arg	Asp	Leu	Arg	Cys	Phe	Arg	Lys	Val	Ser	Cys	Tyr	Ile	Met	Gln
	145				150						155				160	
55	Asp	Asp	Met	Leu	Leu	Pro	His	Leu	Thr	Val	Gln	Glu	Ala	Met	Met	Val
				165					170						175	
60	Ser	Ala	His	Leu	Lys	Leu	Gln	Glu	Lys	Asp	Glu	Gly	Arg	Arg	Glu	Met
			180					185						190		
65	Val	Lys	Glu	Ile	Leu	Thr	Ala	Leu	Gly	Leu	Leu	Ser	Cys	Ala	Asn	Thr
		195						200					205			
70	Arg	Thr	Gly	Ser	Leu	Ser	Gly	Gly	Gln	Arg	Lys	Arg	Leu	Ala	Ile	Ala
	210						215					220				
75	Leu	Glu	Leu	Val	Asn	Asn	Pro	Pro	Val	Met	Phe	Phe	Asp	Glu	Pro	Thr
	225				230						235				240	

EP 1 217 066 A1

	Ser Gly Leu Asp Ser Ala Ser Cys Phe Gln Val Val Ser Leu Met Lys	
	245	250 255
5	Gly Leu Ala Gln Gly Gly Arg Ser Ile Ile Cys Thr Ile His Gln Pro	
	260	265 270
10	Ser Ala Lys Leu Phe Glu Leu Phe Asp Gln Leu Tyr Val Leu Ser Gln	
	275	280 285
	Gly Gln Cys Val Tyr Arg Gly Lys Val Cys Asn Leu Val Pro Tyr Leu	
	290	295 300
15	Arg Asp Leu Gly Leu Asn Cys Pro Thr Tyr His Asn Pro Ala Asp Phe	
	305	310 315 320
20	Val Met Glu Val Ala Ser Gly Glu Tyr Gly Asp Gln Asn Ser Arg Leu	
	325	330 335
	Val Arg Ala Val Arg Glu Gly Met Cys Asp Ser Asp His Lys Arg Asp	
	340	345 350
25	Leu Gly Gly Asp Ala Glu Val Asn Pro Phe Leu Trp His Arg Pro Ser	
	355	360 365
30	Glu Glu Val Lys Gln Thr Lys Arg Leu Lys Gly Leu Arg Lys Asp Ser	
	370	375 380
	Ser Ser Met Glu Gly Cys His Ser Phe Ser Ala Ser Cys Leu Thr Gln	
	385	390 395 400
35	Phe Cys Ile Leu Phe Lys Arg Thr Phe Leu Ser Ile Met Arg Asp Ser	
	405	410 415
40	Val Leu Thr His Leu Arg Ile Thr Ser His Ile Gly Ile Gly Leu Leu	
	420	425 430
	Ile Gly Leu Leu Tyr Leu Gly Ile Gly Asn Glu Thr Lys Lys Val Leu	
	435	440 445
45	Ser Asn Ser Gly Phe Leu Phe Phe Ser Met Leu Phe Leu Met Phe Ala	
	450	455 460
50	Ala Leu Met Pro Thr Val Leu Thr Phe Pro Leu Glu Met Gly Val Phe	
	465	470 475 480
	Leu Arg Glu His Leu Asn Tyr Trp Tyr Ser Leu Lys Ala Tyr Tyr Leu	
	485	490 495
55		

EP 1 217 066 A1

Ala Lys Thr Met Ala Asp Val Pro Phe Gln Ile Met Phe Pro Val Ala
500 505 510

5

Tyr Cys Ser Ile Val Tyr Trp Met Thr Ser Gln Pro Ser Asp Ala Val
515 520 525

10

Arg Phe Val Leu Phe Ala Ala Leu Gly Thr Met Thr Ser Leu Val Ala
530 535 540

Gln Ser Leu Gly Leu Leu Ile Gly Ala Ala Ser Thr Ser Leu Gln Val
545 550 555 560

15

Ala Thr Phe Val Gly Pro Val Thr Ala Ile Pro Val Leu Leu Phe Ser
565 570 575

20

Gly Phe Phe Val Ser Phe Asp Thr Ile Pro Thr Tyr Leu Gln Trp Met
580 585 590

Ser Tyr Ile Ser Tyr Val Arg Tyr Gly Phe Glu Gly Val Ile Leu Ser
595 600 605

25

Ile Tyr Gly Leu Asp Arg Glu Asp Leu His Cys Asp Ile Asp Glu Thr
610 615 620

30

Cys His Phe Gln Lys Ser Glu Ala Ile Leu Arg Glu Leu Asp Val Glu
625 630 635 640

35

Asn Ala Lys Leu Tyr Leu Asp Phe Ile Val Leu Gly Ile Phe Phe Ile
645 650 655

Ser Leu Arg Leu Ile Ala Tyr Leu Val Leu Arg Tyr Lys Ile Arg Ala
660 665 670

40

Glu Arg

45

<210> 79
<211> 655
<212> PRT
<213> Homo sapiens

50

<400> 79
Met Ser Ser Ser Asn Val Glu Val Phe Ile Pro Val Ser Gln Gly Asn
1 5 10 15

55

Thr Asn Gly Phe Pro Ala Thr Val Ser Asn Asp Leu Lys Ala Phe Thr

EP 1 217 066 A1

	20	25	30
5	Glu Gly Ala Val Leu Ser Phe His Asn Ile Cys Tyr Arg Val Lys Leu		
	35	40	45
	Lys Ser Gly Phe Leu Pro Cys Arg Lys Pro Val Glu Lys Glu Ile Leu		
10	50	55	60
	Ser Asn Ile Asn Gly Ile Met Lys Pro Gly Leu Asn Ala Ile Leu Gly		
	65	70	75 80
15	Pro Thr Gly Gly Gly Lys Ser Ser Leu Leu Asp Val Leu Ala Ala Arg		
	85	90	95
	Lys Asp Pro Ser Gly Leu Ser Gly Asp Val Leu Ile Asn Gly Ala Pro		
20	100	105	110
	Arg Pro Ala Asn Phe Lys Cys Asn Ser Gly Tyr Val Val Gln Asp Asp		
	115	120	125
25	Val Val Met Gly Thr Leu Thr Val Arg Glu Asn Leu Gln Phe Ser Ala		
	130	135	140
	Ala Leu Arg Leu Ala Thr Thr Met Thr Asn His Glu Lys Asn Glu Arg		
30	145	150	155 160
	Ile Asn Arg Val Ile Glu Glu Leu Gly Leu Asp Lys Val Ala Asp Ser		
	165	170	175
35	Lys Val Gly Thr Gln Phe Ile Arg Gly Val Ser Gly Gly Glu Arg Lys		
	180	185	190
	Arg Thr Ser Ile Gly Met Glu Leu Ile Thr Asp Pro Ser Ile Leu Ser		
40	195	200	205
	Leu Asp Glu Pro Thr Thr Gly Leu Asp Ser Ser Thr Ala Asn Ala Val		
	210	215	220
45	Leu Leu Leu Leu Lys Arg Met Ser Lys Gln Gly Arg Thr Ile Ile Phe		
	225	230	235 240
	Ser Ile His Gln Pro Arg Tyr Ser Ile Phe Lys Leu Phe Asp Ser Leu		
50	245	250	255
	Thr Leu Leu Ala Ser Gly Arg Leu Met Phe His Gly Pro Ala Gln Glu		
	260	265	270
55	Ala Leu Gly Tyr Phe Glu Ser Ala Gly Tyr His Cys Glu Ala Tyr Asn		

EP 1 217 066 A1

	275	280	285
5	Asn Pro Ala Asp Phe Phe Leu Asp Ile Ile Asn Gly Asp Ser Thr Ala 290	295	300
10	Val Ala Leu Asn Arg Glu Glu Asp Phe Lys Ala Thr Glu Ile Ile Glu 305	310	315 320
	Pro Ser Lys Gln Asp Lys Pro Leu Ile Glu Lys Leu Ala Glu Ile Tyr 325	330	335
15	Val Asn Ser Ser Phe Tyr Lys Glu Thr Lys Ala Glu Leu His Gln Leu 340	345	350
20	Ser Gly Gly Glu Lys Lys Lys Lys Ile Thr Val Phe Lys Glu Ile Ser 355	360	365
	Tyr Thr Thr Ser Phe Cys His Gln Leu Arg Trp Val Ser Lys Arg Ser 370	375	380
25	Phe Lys Asn Leu Leu Gly Asn Pro Gln Ala Ser Ile Ala Gln Ile Ile 385	390	395 400
30	Val Thr Val Val Leu Gly Leu Val Ile Gly Ala Ile Tyr Phe Gly Leu 405	410	415
	Lys Asn Asp Ser Thr Gly Ile Gln Asn Arg Ala Gly Val Leu Phe Phe 420	425	430
35	Leu Thr Thr Asn Gln Cys Phe Ser Ser Val Ser Ala Val Glu Leu Phe 435	440	445
40	Val Val Glu Lys Lys Leu Phe Ile His Glu Tyr Ile Ser Gly Tyr Tyr 450	455	460
	Arg Val Ser Ser Tyr Phe Leu Gly Lys Leu Leu Ser Asp Leu Leu Pro 465	470	475 480
45	Met Arg Met Leu Pro Ser Ile Ile Phe Thr Cys Ile Val Tyr Phe Met 485	490	495
50	Leu Gly Leu Lys Pro Lys Ala Asp Ala Phe Phe Val Met Met Phe Thr 500	505	510
	Leu Met Met Val Ala Tyr Ser Ala Ser Ser Met Ala Leu Ala Ile Ala 515	520	525
55	Ala Gly Gln Ser Val Val Ser Val Ala Thr Leu Leu Met Thr Ile Cys		

EP 1 217 066 A1

	530	535	540	
5	Phe Val Phe Met Met Ile Phe Ser Gly Leu Leu Val Asn Leu Thr Thr			
	545	550	555	560
	Ile Ala Ser Trp Leu Ser Trp Leu Gln Tyr Phe Ser Ile Pro Arg Tyr			
10		565	570	575
	Gly Phe Thr Ala Leu Gln His Asn Glu Phe Leu Gly Gln Asn Phe Cys			
		580	585	590
15	Pro Gly Leu Asn Ala Thr Gly Asn Asn Pro Cys Asn Tyr Ala Thr Cys			
		595	600	605
	Thr Gly Glu Glu Tyr Leu Val Lys Gln Gly Ile Asp Leu Ser Pro Trp			
20		610	615	620
	Gly Leu Trp Lys Asn His Val Ala Leu Ala Cys Met Ile Val Ile Phe			
	625	630	635	640
25	Leu Thr Ile Ala Tyr Leu Lys Leu Leu Phe Leu Lys Lys Tyr Ser			
		645	650	655
30	<210> 80			
	<211> 649			
	<212> PRT			
	<213> Homo sapiens			
35				
	<400> 80			
	Met Gly Asp Leu Ser Ser Leu Thr Pro Gly Gly Ser Met Gly Leu Gln			
	1	5	10	15
40				
	Val Asn Arg Gly Ser Gln Ser Ser Leu Glu Gly Ala Pro Ala Thr Ala			
		20	25	30
	Pro Glu Pro His Ser Leu Gly Ile Leu His Ala Ser Tyr Ser Val Ser			
45		35	40	45
	His Arg Val Arg Pro Trp Trp Asp Ile Thr Ser Cys Arg Gln Gln Trp			
	50	55	60	
50				
	Thr Arg Gln Ile Leu Lys Asp Val Ser Leu Tyr Val Glu Ser Gly Gln			
	65	70	75	80
55				
	Ile Met Cys Ile Leu Gly Ser Ser Gly Ser Gly Lys Thr Thr Leu Leu			
		85	90	95

EP 1 217 066 A1

5	Asp Ala Met Ser Gly Arg Leu Gly Arg Ala Gly Thr Phe Leu Gly Glu	100	105	110
	Val Tyr Val Asn Gly Arg Ala Leu Arg Arg Glu Gln Phe Gln Asp Cys	115	120	125
10	Phe Ser Tyr Val Leu Gln Ser Asp Thr Leu Leu Ser Ser Leu Thr Val	130	135	140
15	Arg Glu Thr Leu His Tyr Thr Ala Leu Leu Ala Ile Arg Arg Gly Asn	145	150	155
	Pro Gly Ser Phe Gln Lys Lys Val Glu Ala Val Met Ala Glu Leu Ser	165	170	175
20	Leu Ser His Val Ala Asp Arg Leu Ile Gly Asn Tyr Ser Leu Gly Gly	180	185	190
25	Ile Ser Thr Gly Glu Arg Arg Arg Val Ser Ile Ala Ala Gln Leu Leu	195	200	205
	Gln Asp Pro Lys Val Met Leu Phe Pro Thr Thr Gly Leu Asp Cys Met	210	215	220
30	Thr Ala Asn Gln Ile Val Val Leu Leu Val Glu Leu Ala Arg Arg Asn	225	230	235
35	Arg Ile Val Val Leu Thr Ile His Gln Pro Arg Ser Glu Leu Phe Gln	245	250	255
	Leu Phe Asp Lys Ile Ala Ile Leu Ser Phe Gly Glu Leu Ile Phe Cys	260	265	270
40	Gly Thr Pro Ala Glu Met Leu Asp Phe Phe Asn Asp Cys Gly Tyr Pro	275	280	285
45	Cys Pro Glu His Ser Asn Pro Phe Asp Phe Tyr Met Asp Leu Thr Ser	290	295	300
	Val Asp Thr Gln Ser Lys Glu Arg Glu Ile Glu Thr Ser Lys Arg Val	305	310	315
50	Gln Met Ile Glu Ser Ala Tyr Lys Lys Ser Ala Ile Cys His Lys Thr	325	330	335
55	Leu Lys Asn Ile Glu Arg Met Lys His Leu Lys Thr Leu Pro Met Val	340	345	350

EP 1 217 066 A1

5	Pro Phe Lys Thr Lys Asp Ser Pro Gly Val Phe Ser Lys Leu Gly Val	355	360	365
	Leu Leu Arg Arg Val Thr Arg Asn Leu Val Arg Asn Lys Leu Ala Val	370	375	380
10	Ile Thr Arg Leu Leu Gln Asn Leu Ile Met Gly Leu Phe Leu Leu Phe	385	390	395
				400
15	Phe Val Leu Arg Val Arg Ser Asn Val Leu Lys Gly Ala Ile Gln Asp	405	410	415
	Arg Val Gly Leu Leu Tyr Gln Phe Val Gly Ala Thr Pro Tyr Thr Gly	420	425	430
20	Met Leu Asn Ala Val Asn Leu Phe Pro Val Leu Arg Ala Val Ser Asp	435	440	445
25	Gln Glu Ser Gln Asp Gly Leu Tyr Gln Lys Trp Gln Met Met Leu Ala	450	455	460
	Tyr Ala Leu His Val Leu Pro Phe Ser Val Val Ala Thr Met Ile Phe	465	470	475
				480
30	Ser Ser Val Cys Tyr Trp Thr Leu Gly Leu His Pro Glu Val Ala Arg	485	490	495
35	Phe Gly Tyr Phe Ser Ala Ala Leu Leu Ala Pro His Leu Ile Gly Glu	500	505	510
	Phe Leu Thr Leu Val Leu Leu Gly Ile Val Gln Asn Pro Asn Ile Val	515	520	525
40	Asn Ser Val Val Ala Leu Leu Ser Ile Ala Gly Val Leu Val Gly Ser	530	535	540
45	Gly Phe Leu Arg Asn Ile Gln Glu Met Pro Ile Pro Phe Lys Ile Ile	545	550	555
				560
	Ser Tyr Phe Thr Phe Gln Lys Tyr Cys Ser Glu Ile Leu Val Val Asn	565	570	575
50	Glu Phe Tyr Gly Leu Asn Phe Thr Cys Gly Ser Ser Asn Val Ser Val	580	585	590
55	Thr Thr Asn Pro Met Cys Ala Phe Thr Gln Gly Ile Gln Phe Ile Glu	595	600	605

EP 1 217 066 A1

5 Lys Thr Cys Pro Gly Ala Thr Ser Arg Phe Thr Met Asn Phe Leu Ile
 610 615 620
 Leu Tyr Ser Phe Ile Pro Ala Leu Val Ile Leu Gly Ile Val Val Phe
 625 630 635 640
 10 Lys Ile Arg Asp His Leu Ile Ser Arg
 645
 15
 <210> 81
 <211> 673
 <212> PRT
 20 <213> Homo sapiens
 <400> 81
 Met Ala Gly Lys Ala Ala Glu Glu Arg Gly Leu Pro Lys Gly Ala Thr
 1 5 10 15
 25 Pro Gln Asp Thr Ser Gly Leu Gln Asp Arg Leu Phe Ser Ser Glu Ser
 20 25 30
 30 Asp Asn Ser Leu Tyr Phe Thr Tyr Ser Gly Gln Pro Asn Thr Leu Glu
 35 40 45
 Val Arg Asp Leu Asn Tyr Gln Val Asp Leu Ala Ser Gln Val Pro Trp
 50 55 60
 35 Phe Glu Gln Leu Ala Gln Phe Lys Met Pro Trp Thr Ser Pro Ser Cys
 65 70 75 80
 40 Gln Asn Ser Cys Glu Leu Gly Ile Gln Asn Leu Ser Phe Lys Val Arg
 85 90 95
 Ser Gly Gln Met Leu Ala Ile Ile Gly Ser Ser Gly Cys Gly Arg Ala
 100 105 110
 45 Ser Leu Leu Asp Val Ile Thr Gly Arg Gly His Gly Gly Lys Ile Lys
 115 120 125
 50 Ser Gly Gln Ile Trp Ile Asn Gly Gln Pro Ser Ser Pro Gln Leu Val
 130 135 140
 Arg Lys Cys Val Ala His Val Arg Gln His Asn Gln Leu Leu Pro Asn
 145 150 155 160
 55

EP 1 217 066 A1

	Leu Thr Val Arg Glu Thr Leu Ala Phe Ile Ala Gln Met Arg Leu Pro	
	165	170 175
5	Arg Thr Phe Ser Gln Ala Gln Arg Asp Lys Arg Val Glu Asp Val Ile	
	180	185 190
10	Ala Glu Leu Arg Leu Arg Gln Cys Ala Asp Thr Arg Val Gly Asn Met	
	195	200 205
	Tyr Val Arg Gly Leu Ser Gly Gly Glu Arg Arg Arg Val Ser Ile Gly	
15	210	215 220
	Val Gln Leu Leu Trp Asn Pro Gly Ile Leu Ile Leu Asp Glu Pro Thr	
	225	230 235 240
20	Ser Gly Leu Asp Ser Phe Thr Ala His Asn Leu Val Lys Thr Leu Ser	
	245	250 255
	Arg Leu Ala Lys Gly Asn Arg Leu Val Leu Ile Ser Leu His Gln Pro	
25	260	265 270
	Arg Ser Asp Ile Phe Arg Leu Phe Asp Leu Val Leu Leu Met Thr Ser	
	275	280 285
30	Gly Thr Pro Ile Tyr Leu Gly Ala Ala Gln His Met Val Gln Tyr Phe	
	290	295 300
	Thr Ala Ile Gly Tyr Pro Cys Pro Arg Tyr Ser Asn Pro Ala Asp Phe	
35	305	310 315 320
	Tyr Val Asp Leu Thr Ser Ile Asp Arg Arg Ser Arg Glu Gln Glu Leu	
	325	330 335
40	Ala Thr Arg Glu Lys Ala Gln Ser Leu Ala Ala Leu Phe Leu Glu Lys	
	340	345 350
	Val Arg Asp Leu Asp Asp Phe Leu Trp Lys Ala Glu Thr Lys Asp Leu	
45	355	360 365
	Asp Glu Asp Thr Cys Val Glu Ser Ser Val Thr Pro Leu Asp Thr Asn	
	370	375 380
50	Cys Leu Pro Ser Pro Thr Lys Met Pro Gly Ala Val Gln Gln Phe Thr	
	385	390 395 400
	Thr Leu Ile Arg Arg Gln Ile Ser Asn Asp Phe Arg Asp Leu Pro Thr	
55	405	410 415

EP 1 217 066 A1

	Leu	Leu	Ile	His	Gly	Ala	Glu	Ala	Cys	Leu	Met	Ser	Met	Thr	Ile	Gly	
					420				425					430			
5	Phe	Leu	Tyr	Phe	Gly	His	Gly	Ser	Ile	Gln	Leu	Ser	Phe	Met	Asp	Thr	
			435					440					445				
10	Ala	Ala	Leu	Leu	Phe	Met	Ile	Gly	Ala	Leu	Ile	Pro	Phe	Asn	Val	Ile	
			450				455					460					
	Leu	Asp	Val	Ile	Ser	Lys	Cys	Tyr	Ser	Glu	Arg	Ala	Met	Leu	Tyr	Tyr	
	465					470					475				480		
15	Glu	Leu	Glu	Asp	Gly	Leu	Tyr	Thr	Thr	Gly	Pro	Tyr	Phe	Phe	Ala	Lys	
					485					490					495		
20	Ile	Leu	Gly	Glu	Leu	Pro	Glu	His	Cys	Ala	Tyr	Ile	Ile	Ile	Tyr	Gly	
					500				505					510			
	Met	Pro	Thr	Tyr	Trp	Leu	Ala	Asn	Leu	Arg	Pro	Gly	Leu	Gln	Pro	Phe	
			515					520					525				
25	Leu	Leu	His	Phe	Leu	Leu	Val	Trp	Leu	Val	Val	Phe	Cys	Cys	Arg	Ile	
			530				535					540					
30	Met	Ala	Leu	Ala	Ala	Ala	Ala	Leu	Leu	Pro	Thr	Phe	His	Met	Ala	Ser	
	545				550					555					560		
	Phe	Phe	Ser	Asn	Ala	Leu	Tyr	Asn	Ser	Phe	Tyr	Leu	Ala	Gly	Gly	Phe	
35					565					570				575			
	Met	Ile	Asn	Leu	Ser	Ser	Leu	Trp	Thr	Val	Pro	Ala	Trp	Ile	Ser	Lys	
				580				585					590				
40	Val	Ser	Phe	Leu	Arg	Trp	Cys	Phe	Glu	Gly	Leu	Met	Lys	Ile	Gln	Phe	
			595					600					605				
	Ser	Arg	Arg	Thr	Tyr	Lys	Met	Pro	Leu	Gly	Asn	Leu	Thr	Ile	Ala	Val	
45			610				615					620					
	Ser	Gly	Asp	Lys	Ile	Leu	Ser	Val	Met	Glu	Leu	Asp	Ser	Tyr	Pro	Leu	
	625				630					635				640			
50	Tyr	Ala	Ile	Tyr	Leu	Ile	Val	Ile	Gly	Leu	Ser	Gly	Gly	Phe	Met	Val	
					645					650				655			
	Leu	Tyr	Tyr	Val	Ser	Leu	Arg	Phe	Ile	Lys	Gln	Lys	Pro	Ser	Gln	Asp	
55					660				665				670				

EP 1 217 066 A1

Trp

5

<210> 82

<211> 590

10

<212> PRT

<213> Streptomyces lincolnensis

<400> 82

15

Met Glu Arg Gly Pro Gln Met Ala Asn Arg Ile Glu Gly Lys Ala Val

1 5 10 15

Asp Lys Thr Ser Ile Lys His Phe Val Lys Leu Ile Arg Ala Ala Lys

20

20 25 30

Pro Arg Tyr Leu Phe Phe Val Ile Gly Ile Val Ala Gly Ile Ile Gly

35 40 45

25

Thr Leu Ile Gln Leu Gln Val Pro Lys Met Val Gln Pro Leu Ile Asn

50 55 60

Ser Phe Gly His Gly Val Asn Gly Gly Lys Val Ala Leu Val Ile Ala

30

65 70 75 80

Leu Tyr Ile Gly Ser Ala Ala Val Ser Ala Ile Ala Ala Ile Val Leu

85 90 95

35

Gly Ile Phe Gly Glu Ser Val Val Lys Asn Leu Arg Thr Arg Val Trp

100 105 110

Asp Lys Met Ile His Leu Pro Val Lys Tyr Phe Asp Glu Val Lys Thr

40

115 120 125

Gly Glu Met Ser Ser Arg Leu Ala Asn Asp Thr Thr Gln Val Lys Asn

130 135 140

45

Leu Ile Ala Asn Ser Ile Pro Gln Ala Phe Thr Ser Ile Leu Leu Leu

145 150 155 160

Val Gly Ser Ile Ile Phe Met Leu Gln Met Gln Trp Arg Leu Thr Leu

50

165 170 175

Ala Met Ile Ile Ala Val Pro Ile Val Met Leu Ile Met Phe Pro Ile

180 185 190

55

Met Thr Phe Gly Gln Lys Ile Gly Trp Thr Arg Gln Asp Ser Leu Ala

EP 1 217 066 A1

	195	200	205
5	Asn Phe Gln Gly Ile Ala Ser Glu Ser Leu Ser Glu Ile Arg Leu Val 210	215	220
10	Lys Ser Ser Asn Ala Glu Lys Gln Ala Ser Lys Lys Ala Glu Asn Asp 225	230	235 240
	Val Asn Ala Leu Tyr Lys Ile Gly Val Lys Glu Ala Val Phe Asp Gly 245	250	255
15	Leu Met Ser Pro Val Met Met Leu Ser Met Met Leu Met Ile Phe Gly 260	265	270
20	Leu Leu Ala Tyr Gly Ile Tyr Leu Ile Ser Thr Gly Val Met Ser Leu 275	280	285
	Gly Thr Leu Leu Gly Met Met Met Tyr Leu Met Asn Leu Ile Gly Val 290	295	300
25	Val Pro Thr Val Ala Thr Phe Phe Thr Glu Leu Ala Lys Ala Ser Gly 305	310	315 320
30	Ser Thr Gly Arg Leu Thr Glu Leu Leu Asp Glu Glu Gln Glu Val Leu 325	330	335
	His Gln Gly Asp Ser Leu Asp Leu Glu Gly Lys Thr Leu Ser Ala His 340	345	350
35	His Val Asp Phe Ala Tyr Asp Asp Ser Glu Gln Ile Leu His Asp Ile 355	360	365
40	Ser Phe Glu Ala Gln Pro Asn Ser Ile Ile Ala Phe Ala Gly Pro Ser 370	375	380
	Gly Gly Gly Lys Ser Thr Ile Phe Ser Leu Leu Glu Arg Phe Tyr Gln 385	390	395 400
45	Pro Thr Ala Gly Glu Ile Thr Ile Gly Gly Gln Pro Ile Asp Ser Val 405	410	415
50	Ser Leu Glu Asn Trp Arg Ser Gln Ile Gly Phe Val Ser Gln Asp Ser 420	425	430
	Ala Ile Met Ala Gly Thr Ile Arg Glu Asn Leu Thr Tyr Gly Leu Glu 435	440	445
55	Gly Asn Phe Thr Asp Glu Asp Leu Trp Gln Val Leu Asp Leu Ala Phe		

EP 1 217 066 A1

	450	455	460
5	Ala Arg Ser Phe Val Glu Asn Met Pro Asp Gln Leu Asn Thr Glu Val		
	465	470	475 480
	Gly Glu Arg Gly Val Lys Ile Ser Gly Gly Gln Arg Gln Arg Leu Ala		
10		485	490 495
	Ile Ala Arg Ala Phe Leu Arg Asn Pro Lys Ile Leu Met Leu Asp Glu		
	500	505	510
15	Ala Thr Ala Ser Leu Asp Ser Glu Ser Glu Ser Met Val Gln Arg Ala		
	515	520	525
	Leu Asp Ser Leu Met Lys Gly Arg Thr Thr Leu Val Ile Ala His Arg		
20	530	535	540
	Leu Ser Thr Ile Val Asp Ala Asp Lys Ile Tyr Phe Ile Glu Lys Gly		
	545	550	555 560
25	Glu Ile Thr Gly Ser Gly Lys His Asn Glu Leu Val Ala Thr His Pro		
	565	570	575
	Leu Tyr Ala Lys Tyr Val Ser Glu Gln Leu Thr Val Gly Gln		
30	580	585	590
35	<210> 83		
	<211> 330		
	<212> PRT		
	<213> Streptomyces peucetius		
40	<400> 83		
	Met Asn Thr Gln Pro Thr Arg Ala Ile Glu Thr Ser Gly Leu Val Lys		
	1	5	10 15
45	Val Tyr Asn Gly Thr Arg Ala Val Asp Gly Leu Asp Leu Asn Val Pro		
	20	25	30
	Ala Gly Leu Val Tyr Gly Ile Leu Gly Pro Asn Gly Ala Gly Lys Ser		
50	35	40	45
	Thr Thr Ile Arg Met Leu Ala Thr Leu Leu Arg Pro Asp Gly Gly Thr		
	50	55	60
55	Ala Arg Val Phe Gly His Asp Val Thr Ser Glu Pro Asp Thr Val Arg		
	65	70	75 80

EP 1 217 066 A1

5	Arg Arg Ile Ser Val Thr Gly Gln Tyr Ala Ser Val Asp Glu Gly Leu	85	90	95
	Thr Gly Thr Glu Asn Leu Val Met Met Gly Arg Leu Gln Gly Tyr Ser	100	105	110
10	Trp Ala Arg Ala Arg Glu Arg Ala Ala Glu Leu Ile Asp Gly Phe Gly	115	120	125
15	Leu Gly Asp Ala Arg Asp Arg Leu Leu Lys Thr Tyr Ser Gly Gly Met	130	135	140
	Arg Arg Arg Leu Asp Ile Ala Ala Ser Ile Val Val Thr Pro Asp Leu	145	150	155
20	Leu Phe Leu Asp Glu Pro Thr Thr Gly Leu Asp Pro Arg Ser Arg Asn	165	170	175
25	Gln Val Trp Asp Ile Val Arg Ala Leu Val Asp Ala Gly Thr Thr Val	180	185	190
	Leu Leu Thr Thr Gln Tyr Leu Asp Glu Ala Asp Gln Leu Ala Asp Arg	195	200	205
30	Ile Ala Val Ile Asp His Gly Arg Val Ile Ala Glu Gly Thr Thr Gly	210	215	220
35	Glu Leu Lys Ser Ser Leu Gly Ser Asn Val Leu Arg Leu Arg Leu His	225	230	235
	Asp Ala Gln Ser Arg Ala Glu Ala Glu Arg Leu Leu Ser Ala Glu Leu	245	250	255
40	Gly Val Thr Ile His Arg Asp Ser Asp Pro Thr Ala Leu Ser Ala Arg	260	265	270
45	Ile Asp Asp Pro Arg Gln Gly Met Arg Ala Leu Ala Glu Leu Ser Arg	275	280	285
	Thr His Leu Glu Val Arg Ser Phe Ser Leu Gly Gln Ser Ser Leu Asp	290	295	300
50	Glu Val Phe Leu Ala Leu Thr Gly His Pro Ala Asp Asp Arg Ser Thr	305	310	315
	Glu Glu Ala Ala Glu Glu Glu Lys Val Ala	325	330	

EP 1 217 066 A1

5 <210> 84
 <211> 569
 <212> PRT
 <213> Streptomyces coelicolor

 10 <400> 84
 Met Gln Asn Ala His Arg Ser Asp Thr Gly Ala Ala Ala Leu Thr Gly
 1 5 10 15
 Thr Pro Glu Lys Leu Leu Pro Thr Gln Pro Glu Thr Gly Ser Phe Gln
 15 20 25 30
 Val Val Leu Asp Asp Val Val Arg Ala Pro Gly Gly Arg Pro Leu Leu
 35 40 45
 20 Asp Gly Val Asn Gln Ser Val Ala Leu Gly Glu Arg Val Gly Ile Ile
 50 55 60
 25 Gly Glu Asn Gly Ser Gly Lys Ser Thr Leu Leu Arg Met Leu Ala Gly
 65 70 75 80
 Val Asp Arg Pro Asp Gly Gly Gln Val Leu Val Arg Ala Pro Gly Gly
 85 90 95
 30 Cys Gly Tyr Leu Pro Gln Thr Pro Asp Leu Pro Pro Glu Asp Thr Val
 100 105 110
 35 Gln Asp Ala Ile Asp His Ala Leu Ala Glu Leu Arg Ser Leu Glu Arg
 115 120 125
 Gly Leu Arg Glu Ala Glu Gln Ala Leu Ala Gly Ala Glu Pro Glu Glu
 130 135 140
 40 Leu Glu Gly Leu Leu Gly Ala Tyr Gly Asp Leu Leu Glu Ala Phe Glu
 145 150 155 160
 45 Ala Arg Asp Gly Tyr Ala Ala Asp Ala Arg Val Asp Ala Ala Met His
 165 170 175
 Gly Leu Gly Leu Ala Gly Ile Thr Gly Asp Arg Arg Leu Gly Ser Leu
 180 185 190
 50 Ser Gly Gly Glu Gln Ala Arg Leu Asn Leu Ala Cys Leu Leu Ala Ala
 195 200 205
 55

EP 1 217 066 A1

	Ser	Pro	Gln	Leu	Met	Leu	Leu	Asp	Glu	Pro	Thr	Asn	His	Leu	Asp	Val	
	210					215						220					
5	Gly	Ala	Leu	Glu	Trp	Leu	Glu	Glu	Arg	Leu	Arg	Ala	His	Arg	Gly	Ser	
	225					230						235				240	
	Val	Leu	Val	Val	Ser	His	Asp	Arg	Val	Phe	Leu	Glu	Arg	Val	Ala	Thr	
10					245					250					255		
	Ala	Leu	Trp	Glu	Val	Asp	Gly	Glu	Arg	Arg	Thr	Val	Asn	Arg	His	Gly	
				260					265					270			
15	Gly	Gly	Tyr	Ala	Gly	Tyr	Leu	Gln	Ala	Lys	Ala	Ala	Ala	Arg	Arg	Arg	
		275					280						285				
	Trp	Glu	Gln	Ala	Tyr	Gln	Asp	Trp	Leu	Glu	Asp	Leu	Ala	Arg	Gln	Arg	
20		290					295					300					
	Glu	Leu	Ala	Arg	Ser	Ala	Ala	Asp	His	Leu	Ala	Thr	Gly	Pro	Arg	Arg	
	305				310						315				320		
25	Asn	Thr	Glu	Arg	Ser	Asn	Gln	Arg	His	Gln	Arg	Asn	Val	Glu	Lys	Gln	
				325					330					335			
30	Ile	Ser	Ala	Arg	Val	Arg	Asn	Ala	Lys	Glu	Arg	Val	Arg	Arg	Leu	Glu	
			340					345					350				
	Glu	Asn	Pro	Val	Pro	Arg	Pro	Pro	Gln	Pro	Met	Arg	Phe	Arg	Ala	Arg	
35		355					360					365					
	Val	Glu	Gly	Gly	Gly	Thr	Val	Gly	Arg	Gly	Gly	Ala	Leu	Ala	Glu	Leu	
		370					375					380					
40	Tyr	Lys	Val	Thr	Val	Gly	Thr	Arg	Leu	Asp	Val	Pro	Ser	Phe	Thr	Val	
	385				390					395					400		
	Asp	Pro	Gly	Glu	Arg	Ile	Leu	Ile	Thr	Gly	His	Asn	Gly	Ala	Gly	Lys	
45				405					410				415				
	Ser	Thr	Leu	Leu	Arg	Val	Leu	Ala	Gly	Asp	Leu	Ala	Pro	Asp	Gln	Gly	
			420					425				430					
50	Glu	Cys	Glu	Arg	Pro	Glu	Arg	Ile	Gly	Trp	Leu	Pro	Gln	Glu	Thr	Glu	
		435					440					445					
	Ile	Thr	Asp	Arg	Gln	Gln	Ser	Leu	Leu	Ala	Ala	Phe	Ala	Ala	Gly	Leu	
55		450					455					460					

EP 1 217 066 A1

Pro Gly Ile Ala Glu Glu His Arg Gly Ala Leu Leu Gly Phe Gly Leu
465 470 475 480

5 Phe Arg Pro Ser Ala Leu Gly Thr Ala Val Gly Asp Leu Ser Thr Gly
485 490 495

Gln Leu Arg Arg Leu Ala Leu Ala Arg Leu Leu Arg Asp Pro Ala Asp
10 500 505 510

Leu Leu Leu Leu Asp Glu Pro Thr Asn His Leu Ser Pro Ala Leu Val
515 520 525

15 Glu Asp Leu Glu Glu Ala Leu Ala His Tyr Arg Gly Ala Leu Val Val
530 535 540

Val Ser His Asp Arg Met Phe Ala Gln Arg Phe Thr Gly Arg Arg Met
20 545 550 555 560

His Met Glu Gly Gly Arg Phe Val Glu
565

25

<210> 85
<211> 1025
30 <212> PRT
<213> Plasmodium falciparum

<400> 85
35 Met Asp Val Ser Asn Tyr Glu Tyr Leu Arg Ser Tyr Gly Ile Lys Asn
1 5 10 15

Glu Leu Lys Arg Lys Arg Thr His Lys Lys Ile Ile Ile Tyr His Leu
40 20 25 30

Leu Asp Ile Ile Ile Phe Phe Leu Leu Phe Phe Ser Cys Tyr Asn Phe
35 40 45

45 Asn Leu Glu Leu Cys Tyr Lys Tyr Glu Lys Ala Ile Phe Tyr Asn Phe
50 55 60

Phe Lys Ser Ser Val Asp Leu Phe Leu Leu Asn Val Ile Arg Ile Ile
50 65 70 75 80

Tyr Thr Val Ile Leu Phe Arg Leu His Lys Lys Leu Thr Glu Leu Asn
85 90 95

55 Thr Leu Gly Lys Val Tyr Val Leu Ser Arg His Ile Thr Gly Ile Leu

EP 1 217 066 A1

	100	105	110
5	Val Ile Leu Asn Val Ile Lys Met Ile Asn Tyr Ser Tyr Val Ile Lys 115 120 125		
10	Ser Glu Asn Pro Leu Tyr Asn Thr Asn Met Tyr Leu Ile Thr Leu Lys 130 135 140		
	Val Leu Phe Met Val Tyr Ser Met Ile Ser Ser Ile Tyr Tyr Tyr Phe 145 150 155 160		
15	Ile Gln Phe Lys Leu Tyr Asn Ile Lys Lys Lys Tyr Ile Ile Ala Arg 165 170 175		
20	Val Glu Leu Glu Lys Ile Leu Ile Asn Asp Ile Lys Ser Lys Lys Tyr 180 185 190		
	Asn Ile Tyr Lys Ser Asp Glu Asn Ser Gly Leu Leu Gly Thr Asp Asn 195 200 205		
25	Asn Ser Thr Ile Met Asn Asn Glu Tyr Leu Asn Leu Asp Tyr Lys Asn 210 215 220		
30	Leu Leu Asp Met Asn Ile Ser Tyr Asn Lys Leu Asn Glu Lys Ile Asn 225 230 235 240		
	Asn Asp Ile Ile Asn Asn Thr Ser Asp Val Gln Glu Lys Asn Met Asp 245 250 255		
35	Tyr Asn Asp Ile His Asn Phe Gln Lys Lys Lys Lys Ser Ser Asn Phe 260 265 / 270		
40	Ala Tyr Leu Asn Phe Phe His Lys Glu Ser Lys Asp Asn Lys Ile Asp 275 280 285		
	Val Lys Glu Ser Phe Leu Asn Lys Arg Tyr Gly Ser Asn Lys Arg Ser 290 295 300		
45	Ser Lys Ile Tyr Asp Asn Asn Asn Asn Asn Asn Asn Asn Ile 305 310 315 320		
50	Asn Ser Lys Ile Asp Tyr Leu Glu Asn Asn Ile Thr Tyr Thr Glu Phe 325 330 335		
	Lys Lys Ile Leu Leu Pro Tyr Leu Trp Pro Ser Lys Arg Ile Asp Met 340 345 350		
55	Lys Gly Asn Ser Ser Ile Leu Arg Thr Tyr Ile Val Leu Ile Phe Leu		

EP 1 217 066 A1

	355	360	365
5	Phe Ile Leu Val Ser Lys Val	Phe Ser Val Ile Ser	Pro Ile Tyr Leu
	370	375	380
10	Gly Trp Ala Ser Asn Glu Val Leu Lys Lys Ser Leu Ser Ser Ser Val		
	385	390	400
	Tyr Tyr Leu Gly Leu Tyr Val Thr Phe Phe Phe Ile Ser Lys Phe Leu		
	405	410	415
15	Lys Glu Val Cys Gly Val Leu Phe Ser Gln Val Gln Gln Ser Ala Phe		
	420	425	430
20	Ile Glu Leu Gln Glu Ser Ile Phe Gln Thr Phe His Asn Leu Ser Tyr		
	435	440	445
	Glu Trp Tyr Ser Ser Lys Asn Ser Gly Gly Ile Met Arg Ile Val Asp		
	450	455	460
25	Arg Gly Thr Glu Ser Ala Asn Asn Leu Met Ser Ser Val Leu Met Tyr		
	465	470	475
30	Ile Ile Pro Ala Thr Ile Glu Gly Leu Ile Thr Cys Ile Ile Phe Ile		
	485	490	495
	Phe Lys Tyr Lys Asn Ser Leu Leu Gly Ser Val Leu Phe Ile Gly Leu		
	500	505	510
35	Thr Leu Tyr Ile Tyr Ser Thr Ile Lys Ile Thr Lys Trp Arg Lys Lys		
	515	520	525
40	Ile Arg Thr Lys Ala Asn Glu Met Asp Asn Val Tyr His Asp Ile Ala		
	530	535	540
	His Asp Ser Leu Thr Asn Tyr Glu Asn Val Lys Tyr Phe Ser Asn Glu		
	545	550	555
45	Lys Phe Glu Ile Lys Lys Phe Cys Asn Ala Leu Ser Asn Tyr His Arg		
	565	570	575
50	Tyr Asn Leu Lys Ile Leu Asn Ser Leu Gly Ile Leu Asn Thr Val Gln		
	580	585	590
	Gln Phe Ile Leu Asn Gly Thr Leu Phe Phe Thr Leu Leu Cys Val Ile		
	595	600	605
55	Tyr Met Ile Val Lys Glu Gly Ser Asp Pro Gly Thr Phe Ile Ser Val		

EP 1 217 066 A1

	610	615	620
5	Val Val Tyr Thr Ser Asn Val Phe Ala Pro Leu Ser Ile Leu Gly Thr 625	630	635 640
10	Leu Tyr Ala Thr Ile Ile Lys Ser Phe Thr Asp Ile Ser Asp Leu Ile 645	650	655
15	Asp Ile Leu Arg Asp Lys Ile Asp Ile Ser Asn Asp Lys Asn Leu Lys 660	665	670
20	Asn Phe Asp Leu Thr Ser Gln Glu Lys Lys Phe Gly Val Ser Ile Glu 675	680	685
25	Phe Asn Asn Val His Phe Asn Tyr Pro Thr Gln Pro Leu His Thr Ser 690	695	700
30	Leu Lys Asp Ile Asn Ile Tyr Ile Lys Pro Gly Thr Thr Cys Ala Leu 705	710	715 720
35	Val Gly His Thr Gly Ser Gly Lys Thr Thr Ile Ser Lys Leu Leu Tyr 725	730	735
40	Arg Phe Tyr Asp Ser Lys Gly Glu Ile Lys Ile Gly Gly Arg Asn Ile 740	745	750
45	Asn Glu Tyr Thr Arg Asn Ser Ile Arg Asn Ile Ile Gly Ile Val Pro 755	760	765
50	Gln Asp Thr Ile Leu Phe Asn Glu Ser Ile Lys Tyr Asn Ile Leu Tyr 770	775	780
55	Gly Lys Leu Asp Ala Thr Glu Glu Glu Leu Ile Gln Ala Val Lys Ser 785	790	795 800
60	Ala Gln Leu Tyr Asp Phe Ile Gln Ser Leu Pro Lys Lys Trp Asp Thr 805	810	815
65	Leu Val Gly Asp Lys Gly Val Lys Leu Ser Gly Gly Glu Arg Gln Arg 820	825	830
70	Ile Ser Ile Ala Arg Cys Leu Leu Lys Asp Pro Lys Ile Val Ile Phe 835	840	845
75	Asp Glu Ala Thr Ser Ser Leu Asp Ser Arg Thr Glu Tyr Leu Phe Gln 850	855	860
80	Lys Ala Val Glu Asp Leu Arg Lys Asn Arg Thr Ile Ile Ile Ala		

EP 1 217 066 A1

	865		870		875		880									
5	His	Lys	Leu	Cys	Thr	Ile	Thr	Thr	Ala	Glu	Leu	Ile	Ile	Leu	Leu	Asn
					885					890					895	
	Lys	Gly	Lys	Ile	Ile	Glu	Arg	Gly	Thr	His	Leu	Asp	Leu	Leu	Lys	Cys
10				900				905					910			
	Asn	Gly	Glu	Tyr	Thr	Glu	Met	Trp	Asn	Met	Gln	Ser	Lys	Ser	Asn	Glu
			915					920					925			
15	Pro	His	Thr	Glu	Thr	Asn	Ser	Ser	Ile	Asp	Lys	Asp	Asp	Val	Asn	Lys
		930					935					940				
	Asn	Asn	Asn	Lys	Asn	Asn	Asp	Val	Ile	Leu	Asn	Thr	Cys	Lys	Asn	Asp
20		945				950				955					960	
	Ile	Thr	Thr	Ser	Phe	Arg	Ser	Asn	Ser	Glu	Lys	Ser	Ser	Gln	Glu	Phe
					965					970					975	
25	Ser	Asp	Ala	Ser	Asn	His	Ile	Lys	Gln	Ser	Lys	Thr	Ser	Asn	Asp	His
				980					985					990		
	Asn	Asn	Asn	Ile	Asn	Val	His	Lys	Lys	Asn	Glu	Gln	Glu	Gln	Leu	Phe
30			995				1000					1005				
	Leu	Thr	Asn	Asp	Lys	Thr	Asp	Met	Asp	Asp	Asn	Met	Asn	Asn	Lys	Lys
		1010					1015					1020				
35	Lys															
	1025															
40																
	<210>	86														
	<211>	1419														
	<212>	PRT														
45	<213>	Plasmodium falciparum														
	<400>	86														
	Met	Gly	Lys	Glu	Gln	Lys	Glu	Lys	Lys	Asp	Gly	Asn	Leu	Ser	Ile	Lys
50		1				5				10					15	
	Glu	Glu	Val	Glu	Lys	Glu	Leu	Asn	Lys	Lys	Ser	Thr	Ala	Glu	Leu	Phe
				20					25					30		
55	Arg	Lys	Ile	Lys	Asn	Glu	Lys	Ile	Ser	Phe	Phe	Leu	Pro	Phe	Lys	Cys
				35					40					45		

EP 1 217 066 A1

5 Leu Pro Ala Gln His Arg Lys Leu Leu Phe Ile Ser Phe Val Cys Ala
 50 55 60

 Val Leu Ser Gly Gly Thr Leu Pro Phe Phe Ile Ser Val Phe Gly Val
 65 70 75 80
 10 Ile Leu Lys Asn Met Asn Leu Gly Asp Asp Ile Asn Pro Ile Ile Leu
 85 90 95

 Ser Leu Val Ser Ile Gly Leu Val Gln Phe Ile Leu Ser Met Ile Ser
 15 100 105 110

 Ser Tyr Cys Met Asp Val Ile Thr Ser Lys Ile Leu Lys Thr Leu Lys
 115 120 125
 20 Leu Glu Tyr Leu Arg Ser Val Phe Tyr Gln Asp Gly Gln Phe His Asp
 130 135 140

 Asn Asn Pro Gly Ser Lys Leu Arg Ser Asp Leu Asp Phe Tyr Leu Glu
 25 145 150 155 160

 Gln Val Ser Ser Gly Ile Gly Thr Lys Phe Ile Thr Ile Phe Thr Tyr
 165 170 175
 30 Ala Ser Ser Phe Leu Gly Leu Tyr Ile Trp Ser Leu Ile Lys Asn Ala
 180 185 190

 Arg Leu Thr Leu Cys Ile Thr Cys Val Phe Pro Leu Ile Tyr Val Cys
 35 195 200 205

 Gly Val Ile Cys Asn Lys Lys Val Lys Leu Asn Lys Lys Thr Ser Leu
 210 215 220
 40 Leu Tyr Asn Asn Asn Thr Met Ser Ile Ile Glu Glu Ala Leu Met Gly
 225 230 235 240

 Ile Arg Thr Val Ala Ser Tyr Cys Gly Glu Lys Thr Ile Leu Asn Lys
 45 245 250 255

 Phe Asn Leu Ser Glu Thr Phe Tyr Ser Lys Tyr Ile Leu Lys Ala Asn
 260 265 270
 50 Phe Val Glu Ala Leu His Ile Gly Leu Ile Asn Gly Leu Ile Leu Val
 275 280 285

 Ser Tyr Ala Phe Gly Phe Trp Tyr Gly Thr Arg Ile Ile Ile Asn Ser
 55 290 295 300

EP 1 217 066 A1

5	Ala Thr Asn Gln Tyr Pro Asn Asn Asp Phe Asn Gly Ala Ser Val Ile	305	310	315	320
	Ser Ile Leu Leu Gly Val Leu Ile Ser Met Phe Met Leu Thr Ile Ile	325	330	335	
10	Leu Pro Asn Ile Thr Glu Tyr Met Lys Ala Leu Glu Ala Thr Asn Ser	340	345	350	
15	Leu Tyr Glu Ile Ile Asn Arg Lys Pro Leu Val Glu Asn Asn Asp Asp	355	360	365	
	Gly Glu Thr Leu Pro Asn Ile Lys Lys Ile Glu Phe Lys Asn Val Arg	370	375	380	
20	Phe His Tyr Asp Thr Arg Lys Asp Val Glu Ile Tyr Lys Asp Leu Ser	385	390	395	400
25	Phe Thr Leu Lys Glu Gly Lys Thr Tyr Ala Phe Val Gly Glu Ser Gly	405	410	415	
	Cys Gly Lys Ser Thr Ile Leu Lys Leu Ile Glu Arg Leu Tyr Asp Pro	420	425	430	
30	Thr Glu Gly Asp Ile Ile Val Asn Asp Ser His Asn Leu Lys Asp Ile	435	440	445	
35	Asn Leu Lys Trp Trp Arg Ser Lys Ile Gly Val Val Ser Gln Asp Pro	450	455	460	
	Leu Leu Phe Ser Asn Ser Ile Lys Asn Asn Ile Lys Tyr Ser Leu Tyr	465	470	475	480
40	Ser Leu Lys Asp Leu Glu Ala Met Glu Asn Tyr Tyr Glu Glu Asn Thr	485	490	495	
45	Asn Asp Thr Tyr Glu Asn Lys Asn Phe Ser Leu Ile Ser Asn Ser Met	500	505	510	
	Thr Ser Asn Glu Leu Leu Glu Met Lys Lys Glu Tyr Gln Thr Ile Lys	515	520	525	
50	Asp Ser Asp Val Val Asp Val Ser Lys Lys Val Leu Ile His Asp Phe	530	535	540	
55	Val Ser Ser Leu Pro Asp Lys Tyr Asp Thr Leu Val Gly Ser Asn Ala	545	550	555	560

EP 1 217 066 A1

5	Ser Lys Leu Ser Gly Gly Gln Lys Gln Arg Ile Ser Ile Ala Arg Ala	565	570	575
	Ile Met Arg Asn Pro Lys Ile Leu Ile Leu Asp Glu Ala Thr Ser Ser	580	585	590
10	Leu Asp Asn Lys Ser Glu Tyr Leu Val Gln Lys Thr Ile Asn Asn Leu	595	600	605
15	Lys Gly Asn Glu Asn Arg Ile Thr Ile Ile Ile Ala His Arg Leu Ser	610	615	620
	Thr Ile Arg Tyr Ala Asn Thr Ile Phe Val Leu Ser Asn Arg Glu Arg	625	630	635
20	Ser Asp Asn Asn Asn Asn Asn Asn Asn Asp Asp Asn Asn Asn Asn Asn	645	650	655
25	Asn Asn Asn Asn Asn Lys Ile Asn Asn Glu Gly Ser Tyr Ile Ile Glu	660	665	670
	Gln Gly Thr His Asp Ser Leu Met Lys Asn Lys Asn Gly Ile Tyr His	675	680	685
30	Leu Met Ile Asn Asn Gln Lys Ile Ser Ser Asn Lys Ser Ser Asn Asn	690	695	700
35	Gly Asn Asp Asn Gly Ser Asp Asn Lys Ser Ser Ala Tyr Lys Asp Ser	705	710	715
	Asp Thr Gly Asn Asp Ala Asp Asn Met Asn Ser Leu Ser Ile His Glu	725	730	735
40	Asn Glu Asn Ile Ser Asn Asn Arg Asn Cys Lys Asn Thr Ala Glu Asn	740	745	750
45	Glu Lys Glu Glu Lys Val Pro Phe Phe Lys Arg Met Phe Arg Arg Lys	755	760	765
	Lys Lys Ala Pro Asn Asn Leu Arg Ile Ile Tyr Lys Glu Ile Phe Ser	770	775	780
50	Tyr Lys Lys Asp Val Thr Ile Ile Phe Phe Ser Ile Leu Val Ala Gly	785	790	795
	Gly Leu Tyr Pro Val Phe Ala Leu Leu Tyr Ala Arg Tyr Val Ser Thr	805	810	815

EP 1 217 066 A1

5	Leu Phe Asp Phe Ala Asn Leu Glu Tyr Asn Ser Asn Lys Tyr Ser Ile	820	825	830
	Tyr Ile Leu Leu Ile Ala Ile Ala Met Phe Ile Ser Glu Thr Leu Lys	835	840	845
10	Asn Tyr Tyr Asn Asn Lys Ile Gly Glu Lys Val Glu Lys Thr Met Lys	850	855	860
15	Arg Arg Leu Phe Glu Asn Ile Leu Tyr Gln Glu Met Ser Phe Phe Asp	865	870	875
	Gln Asp Lys Asn Thr Pro Gly Val Leu Ser Ala His Ile Asn Arg Asp	885	890	895
20	Val His Leu Leu Lys Thr Gly Leu Val Asn Asn Ile Val Ile Phe Ser	900	905	910
25	His Phe Ile Met Leu Phe Leu Val Ser Met Val Met Ser Phe Tyr Phe	915	920	925
	Cys Pro Ile Val Ala Ala Val Leu Thr Phe Ile Tyr Phe Ile Asn Met	930	935	940
30	Arg Val Phe Ala Val Arg Ala Arg Leu Thr Lys Ser Lys Glu Ile Glu	945	950	955
35	Lys Lys Glu Asn Met Ser Ser Gly Val Phe Ala Phe Ser Ser Asp Asp	965	970	975
	Glu Met Phe Lys Asp Pro Ser Phe Leu Ile Gln Glu Ala Phe Tyr Asn	980	985	990
40	Met His Thr Val Ile Asn Tyr Gly Leu Glu Asp Tyr Phe Cys Asn Leu	995	1000	1005
45	Ile Glu Lys Ala Ile Asp Tyr Lys Asn Lys Gly Gln Lys Arg Arg Ile	1010	1015	1020
	Ile Val Asn Ala Ala Leu Trp Gly Phe Ser Gln Ser Ala Gln Leu Phe	1025	1030	1035
50	Ile Asn Ser Phe Ala Tyr Trp Phe Gly Ser Phe Leu Ile Lys Arg Gly	1045	1050	1055
55	Thr Ile Leu Val Asp Asp Phe Met Lys Ser Leu Phe Thr Phe Ile Phe	1060	1065	1070

EP 1 217 066 A1

5 Thr Gly Ser Tyr Ala Gly Lys Leu Met Ser Leu Lys Gly Asp Ser Glu
 1075 1080 1085
 Asn Ala Lys Leu Ser Phe Glu Lys Tyr Tyr Pro Leu Met Ile Arg Lys
 1090 1095 1100
 10 Ser Asn Ile Asp Val Arg Asp Asp Gly Gly Ile Arg Ile Asn Lys Asn
 1105 1110 1115 1120
 15 Leu Ile Lys Gly Lys Val Asp Ile Lys Asp Val Asn Phe Arg Tyr Ile
 1125 1130 1135
 Ser Arg Pro Asn Val Pro Ile Tyr Lys Asn Leu Ser Phe Thr Cys Asp
 1140 1145 1150
 20 Ser Lys Lys Thr Thr Ala Ile Val Gly Glu Thr Gly Ser Gly Lys Ser
 1155 1160 1165
 25 Thr Phe Met Asn Leu Leu Leu Arg Phe Tyr Asp Leu Lys Asn Asp His
 1170 1175 1180
 Ile Ile Leu Lys Asn Asp Met Thr Asn Phe Gln Asp Tyr Gln Asn Asn
 1185 1190 1195 1200
 30 Asn Asn Asn Ser Leu Val Leu Lys Asn Val Asn Glu Phe Ser Asn Gln
 1205 1210 1215
 35 Ser Gly Ser Ala Glu Asp Tyr Thr Val Phe Asn Asn Asn Gly Glu Ile
 1220 1225 1230
 Leu Leu Asp Asp Ile Asn Ile Cys Asp Tyr Asn Leu Arg Asp Leu Arg
 1235 1240 1245
 40 Asn Leu Phe Ser Ile Val Ser Gln Glu Pro Met Leu Phe Asn Met Ser
 1250 1255 1260
 45 Ile Tyr Glu Asn Ile Lys Phe Gly Arg Glu Asp Ala Thr Leu Glu Asp
 1265 1270 1275 1280
 Val Lys Arg Val Ser Lys Phe Ala Ala Ile Asp Glu Phe Ile Glu Ser
 1285 1290 1295
 50 Leu Pro Asn Lys Tyr Asp Thr Asn Val Gly Pro Tyr Gly Lys Ser Leu
 1300 1305 1310
 55 Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala Leu Leu Arg
 1315 1320 1325

EP 1 217 066 A1

5 Glu Pro Lys Ile Leu Leu Leu Asp Glu Ala Thr Ser Ser Leu Asp Ser
 1330 1335 1340

 Asn Ser Glu Lys Leu Ile Glu Lys Thr Ile Val Asp Ile Lys Asp Lys
 1345 1350 1355 1360

10 Ala Asp Lys Thr Ile Ile Thr Ile Ala His Arg Ile Ala Ser Ile Lys
 1365 1370 1375

 Arg Ser Asp Lys Ile Val Val Phe Asn Asn Pro Asp Arg Asn Gly Thr
15 1380 1385 1390

 Phe Val Gln Ser His Gly Thr His Asp Glu Leu Leu Ser Ala Gln Asp
 1395 1400 1405

20 Gly Ile Tyr Lys Lys Tyr Val Lys Leu Ala Lys
 1410 1415

25 <210> 87
 <211> 1548
 <212> PRT
30 <213> Leishmania tarentolae

 <400> 87
 Met Val Asp Asn Gly His Val Thr Ile Ala Met Ala Asp Leu Gly Thr
 1 5 10 15

35 Val Val Glu Ile Ala Gln Val Arg Cys Gln Gln Glu Ala Gln Arg Lys
 20 25 30

40 Phe Ala Glu Gln Leu Asp Glu Leu Trp Gly Gly Glu Pro Ala Tyr Thr
 35 40 45

 Pro Thr Val Glu Asp Gln Ala Ser Trp Phe Gln Gln Leu Tyr Tyr Gly
 50 55 60

45 Trp Ile Gly Asp Tyr Ile Tyr Lys Ala Ala Ala Gly Asn Ile Thr Glu
 65 70 75 80

50 Ala Asp Leu Pro Pro Pro Thr Arg Ser Thr Arg Thr Tyr His Ile Gly
 85 90 95

 Arg Lys Leu Ser Arg Gln Ala His Ala Asp Ile Asp Ala Ser Arg Arg
55 100 105 110

EP 1 217 066 A1

	Trp	Gln	Gly	Tyr	Ile	Gly	Cys	Glu	Val	Val	Tyr	Lys	Ser	Glu	Ala	Glu	
5	Ala	Lys	Gly	Val	Leu	Arg	Trp	Val	Gly	His	Leu	Gln	Gln	Ser	Asp	Tyr	
10	Pro	Arg	Ser	Leu	Val	Ala	Gly	Val	Glu	Trp	Arg	Met	Pro	Pro	Arg	His	
	Arg	Arg	Leu	Ala	Val	Leu	Gly	Ser	Ala	Ala	Ala	Leu	His	Asn	Gly	Val	
15	Val	His	Gly	Glu	Arg	Leu	Phe	Trp	Pro	His	Glu	Asp	Asn	Tyr	Leu	Cys	
20	Ser	Cys	Glu	Pro	Val	Glu	Gln	Leu	Tyr	Val	Lys	Ser	Lys	Tyr	Asn	Leu	
	Ile	Pro	Pro	Arg	Pro	Pro	Pro	Ser	Pro	Asp	Leu	Leu	Arg	Thr	Leu	Phe	
25	Lys	Val	His	Trp	Tyr	His	Val	Trp	Ala	Gln	Ile	Leu	Pro	Lys	Leu	Leu	
30	Ser	Asp	Val	Thr	Ala	Leu	Met	Leu	Pro	Val	Leu	Leu	Glu	Tyr	Phe	Val	
	Lys	Tyr	Leu	Asn	Ala	Asp	Asn	Ala	Thr	Trp	Gly	Trp	Gly	Leu	Gly	Leu	
35	Ala	Leu	Thr	Ile	Phe	Leu	Thr	Asn	Val	Ile	Gln	Ser	Cys	Ser	Ala	His	
40	Lys	Tyr	Asp	His	Ile	Ser	Ile	Arg	Thr	Ala	Ala	Leu	Phe	Glu	Thr	Ser	
	Ser	Met	Ala	Leu	Leu	Phe	Glu	Lys	Cys	Phe	Thr	Val	Ser	Arg	Arg	Ser	
45	Leu	Gln	Arg	Pro	Asp	Met	Ser	Val	Gly	Arg	Ile	Met	Asn	Met	Val	Gly	
50	Asn	Asp	Val	Asp	Asn	Ile	Gly	Ser	Leu	Asn	Trp	Tyr	Val	Met	Tyr	Phe	
	Trp	Ser	Ala	Pro	Leu	Gln	Leu	Val	Leu	Cys	Leu	Leu	Leu	Leu	Ile	Arg	
55																	

EP 1 217 066 A1

	Leu Val Gly Trp Leu Arg Val Pro Gly Met Ala Val Leu Phe Val Thr	
	370	380
5	Leu Pro Leu Gln Ala Val Ile Ser Lys His Val Gln Asp Val Ser Glu	
	385	400
10	Arg Met Ala Ser Val Val Asp Leu Arg Ile Lys Arg Thr Asn Glu Leu	
	405	415
15	Leu Ser Gly Val Arg Ile Val Lys Phe Met Gly Trp Glu Pro Val Phe	
	420	430
	Leu Ala Arg Ile Gln Asp Ala Arg Ser Arg Glu Leu Arg Cys Leu Arg	
	435	445
20	Asp Val His Val Ala Asn Val Phe Phe Met Phe Val Asn Asp Ala Thr	
	450	460
25	Pro Thr Leu Val Ile Ala Val Val Phe Ile Leu Tyr His Val Ser Gly	
	465	480
	Lys Val Leu Lys Pro Glu Val Val Phe Pro Thr Ile Ala Leu Leu Asn	
	485	495
30	Thr Met Arg Val Ser Phe Phe Met Ile Pro Ile Ile Ile Ser Ser Ile	
	500	510
35	Leu Gln Cys Phe Val Ser Ala Lys Arg Val Thr Ala Phe Ile Glu Cys	
	515	525
	Pro Asp Thr His Ser Gln Val Gln Asp Ile Ala Ser Ile Asp Val Pro	
	530	540
40	Asp Ala Ala Ala Ile Phe Lys Gly Ala Ser Ile His Thr Tyr Leu Pro	
	545	560
45	Val Lys Leu Pro Arg Cys Lys Ser Arg Leu Thr Ala Met Gln Arg Ser	
	565	575
	Thr Leu Trp Phe Arg Arg Arg Gly Val Pro Glu Thr Glu Trp Tyr Glu	
	580	590
50	Val Asp Ser Pro Asp Ala Ser Ala Ser Ser Leu Ala Val His Ser Thr	
	595	605
55	Thr Val His Met Gly Ser Thr Gln Thr Val Ile Thr Asp Ser Asp Gly	
	610	620

EP 1 217 066 A1

	Ala Ala Gly Glu Asp Glu Lys Gly Glu Val Glu Glu Gly Asp Arg Glu	
	625	630 635 640
5	Tyr Tyr Gln Leu Val Ser Lys Gly Leu Leu Arg Asn Val Ser Leu Thr	
	645	650 655
10	Ile Pro Lys Gly Lys Leu Thr Met Val Ile Gly Ser Thr Gly Ser Gly	
	660	665 670
	Lys Ser Thr Leu Leu Gly Ala Leu Met Gly Glu Tyr Ser Val Glu Ser	
	675	680 685
15	Gly Glu Leu Trp Ala Glu Arg Ser Ile Ala Tyr Val Pro Gln Gln Ala	
	690	695 700
20	Trp Ile Met Asn Ala Thr Leu Arg Gly Asn Ile Leu Phe Phe Asp Glu	
	705	710 715 720
	Glu Arg Ala Glu Asp Leu Gln Asp Val Ile Arg Cys Cys Gln Leu Glu	
	725	730 735
25	Ala Asp Leu Ala Gln Phe Cys Gly Gly Leu Asp Thr Glu Ile Gly Glu	
	740	745 750
30	Met Gly Val Asn Leu Ser Gly Gly Gln Lys Ala Arg Val Ser Leu Ala	
	755	760 765
	Arg Ala Val Tyr Ala Asn Arg Asp Val Tyr Leu Leu Asp Asp Pro Leu	
	770	775 780
35	Ser Ala Leu Asp Ala His Val Gly Gln Arg Ile Val Gln Asp Val Ile	
	785	790 795 800
40	Leu Gly Arg Leu Arg Gly Lys Thr Arg Val Leu Ala Thr His Gln Ile	
	805	810 815
	His Leu Leu Pro Leu Ala Asp Tyr Ile Val Val Leu Gln His Gly Ser	
	820	825 830
45	Ile Val Phe Ala Gly Asp Phe Ala Ala Phe Ser Ala Thr Ala Leu Glu	
	835	840 845
50	Glu Thr Leu Arg Gly Glu Leu Lys Gly Ser Lys Asp Val Glu Ser Cys	
	850	855 860
	Ser Ser Asp Val Asp Thr Glu Ser Ala Thr Ala Glu Thr Ala Pro Tyr	
	865	870 875 880
55		

EP 1 217 066 A1

	Val	Ala	Lys	Ala	Lys	Gly	Leu	Asn	Ala	Glu	Gln	Glu	Thr	Ser	Leu	Ala	
					885					890					895		
5	Gly	Gly	Glu	Asp	Pro	Leu	Arg	Ser	Asp	Val	Glu	Ala	Gly	Arg	Leu	Met	
				900				905						910			
10	Thr	Thr	Glu	Glu	Lys	Ala	Thr	Gly	Lys	Val	Pro	Trp	Ser	Thr	Tyr	Val	
			915					920					925				
	Ala	Tyr	Leu	Lys	Ser	Cys	Gly	Gly	Leu	Glu	Ala	Trp	Gly	Cys	Leu	Leu	
		930					935					940					
15	Ala	Thr	Phe	Ala	Leu	Thr	Glu	Cys	Val	Thr	Ala	Ala	Ser	Ser	Val	Trp	
	945				950					955					960		
20	Leu	Ser	Ile	Trp	Ser	Thr	Gly	Ser	Leu	Met	Trp	Ser	Ala	Asp	Thr	Tyr	
				965					970					975			
	Leu	Tyr	Val	Tyr	Leu	Phe	Ile	Val	Phe	Leu	Glu	Ile	Phe	Gly	Ser	Pro	
			980					985					990				
25	Leu	Arg	Phe	Phe	Leu	Cys	Tyr	Tyr	Leu	Ile	Arg	Ile	Gly	Ser	Arg	Asn	
		995					1000					1005					
30	Met	His	Arg	Asp	Leu	Leu	Glu	Ser	Ile	Gly	Val	Ala	Arg	Met	Ser	Phe	
		1010				1015				1020							
	Phe	Asp	Thr	Thr	Pro	Val	Gly	Arg	Val	Leu	Asn	Arg	Phe	Thr	Lys	Asp	
35	1025				1030					1035				1040			
	Met	Ser	Ile	Leu	Asp	Asn	Thr	Leu	Asn	Asp	Gly	Tyr	Leu	Tyr	Leu	Leu	
				1045				1050					1055				
40	Glu	Tyr	Phe	Phe	Ser	Met	Cys	Ser	Thr	Val	Ile	Ile	Met	Val	Val	Val	
			1060					1065				1070					
	Gln	Pro	Phe	Val	Leu	Val	Ala	Ile	Val	Pro	Cys	Val	Tyr	Ser	Tyr	Tyr	
45		1075					1080					1085					
	Lys	Leu	Met	Gln	Val	Tyr	Asn	Ala	Ser	Asn	Arg	Glu	Thr	Arg	Arg	Ile	
		1090				1095					1100						
50	Lys	Ser	Ile	Ala	His	Ser	Pro	Val	Phe	Thr	Leu	Leu	Glu	Glu	Ser	Leu	
	1105				1110					1115				1120			
	Gln	Gly	Gln	Arg	Thr	Ile	Ala	Thr	Tyr	Gly	Lys	Leu	His	Leu	Val	Leu	
55				1125					1130					1135			

EP 1 217 066 A1

Gln Glu Ala Leu Gly Arg Leu Asp Val Val Tyr Ser Ala Leu Tyr Met
1140 1145 1150

5 Gln Asn Val Ser Asn Arg Trp Leu Gly Val Arg Leu Glu Phe Leu Ser
1155 1160 1165

10 Cys Val Val Thr Phe Met Val Ala Phe Ile Gly Val Ile Gly Lys Met
1170 1175 1180

Glu Gly Ala Ser Ser Gln Asn Ile Gly Leu Ile Ser Leu Ser Leu Thr
1185 1190 1195 1200

15 Met Ser Met Thr Leu Thr Glu Thr Leu Asn Trp Leu Val Arg Gln Val
1205 1210 1215

20 Ala Met Val Glu Ala Asn Met Asn Ser Val Glu Arg Val Leu His Tyr
1220 1225 1230

Thr Gln Glu Val Glu His Glu His Val Pro Glu Met Gly Glu Leu Val
1235 1240 1245

25 Ala Gln Leu Val Arg Ser Glu Ser Gly Arg Gly Ala Asn Val Thr Glu
1250 1255 1260

30 Thr Val Val Ile Glu Ser Ala Gly Ala Ala Ser Ser Ala Leu His Pro
1265 1270 1275 1280

Val Gln Ala Gly Ser Leu Val Leu Glu Gly Val Gln Met Arg Tyr Arg
1285 1290 1295

35 Glu Gly Leu Pro Leu Val Leu Arg Gly Val Ser Phe Gln Ile Ala Pro
1300 1305 1310

40 Arg Glu Lys Val Gly Ile Val Gly Arg Thr Gly Ser Gly Lys Ser Thr
1315 1320 1325

Leu Leu Leu Thr Phe Met Arg Met Val Glu Val Cys Gly Gly Val Ile
1330 1335 1340

45 His Val Asn Gly Arg Glu Met Ser Ala Tyr Gly Leu Arg Glu Leu Arg
1345 1350 1355 1360

50 Arg His Phe Ser Met Ile Pro Gln Asp Pro Val Leu Phe Asp Gly Thr
1365 1370 1375

Val Arg Gln Asn Val Asp Pro Phe Leu Glu Ala Ser Ser Ala Glu Val
1380 1385 1390

55

EP 1 217 066 A1

Trp Ala Ala Leu Glu Leu Val Gly Leu Arg Glu Arg Val Ala Ser Glu
1395 1400 1405

5 Ser Glu Gly Ile Asp Ser Arg Val Leu Glu Gly Gly Ser Asn Tyr Ser
1410 1415 1420

10 Val Gly Gln Arg Gln Leu Met Cys Met Ala Arg Ala Leu Leu Lys Arg
1425 1430 1435 1440

Gly Ser Gly Phe Ile Leu Met Asp Glu Ala Thr Ala Asn Ile Asp Pro
1445 1450 1455

15 Ala Leu Asp Arg Gln Ile Gln Ala Thr Val Met Ser Ala Phe Ser Ala
1460 1465 1470

20 Tyr Thr Val Ile Thr Ile Ala His Arg Leu His Thr Val Ala Gln Tyr
1475 1480 1485

Asp Lys Ile Ile Val Met Asp His Gly Val Val Ala Glu Met Gly Ser
1490 1495 1500

25 Pro Arg Glu Leu Val Met Asn His Gln Ser Met Phe His Ser Met Val
1505 1510 1515 1520

30 Glu Ser Leu Gly Ser Arg Gly Ser Lys Asp Phe Tyr Glu Leu Leu Met
1525 1530 1535

Gly Arg Arg Ile Val Gln Pro Ala Val Leu Ser Asp
1540 1545

35

<210> 88
40 <211> 1530
<212> PRT
<213> Schizosaccharomyces pombe

<400> 88

45 Met Asn Gln Asn Ser Asp Thr Thr His Gly Gln Ala Leu Gly Ser Thr
1 5 10 15

Leu Asn His Thr Thr Glu Val Thr Arg Ile Ser Asn Ser Ser Asp His
50 20 25 30

Phe Glu Asp Ser Ser Ser Asn Val Asp Glu Ser Leu Asp Ser Ser Asn
35 40 45

55 Pro Ser Ser Asn Glu Lys Ala Ser His Thr Asn Glu Glu Tyr Arg Ser

EP 1 217 066 A1

	50	55	60
5	Lys Gly Asn Gln Ser Tyr Val Pro Ser Ser Ser Asn Glu Pro Ser Pro		
	65	70	75 80
	Glu Ser Ser Ser Asn Ser Asp Ser Ser Ser Ser Asp Asp Ser Ser Val		
10		85	90 95
	Asp Arg Leu Ala Gly Asp Pro Phe Glu Leu Gly Glu Asn Phe Asn Leu		
	100	105	110
15	Lys His Tyr Leu Arg Ala Tyr Lys Asp Ser Leu Gln Arg Asp Asp Ile		
	115	120	125
	Ile Thr Arg Ser Ser Gly Val Cys Met Arg Asp His Ser Val Tyr Gly		
20	130	135	140
	Val Gly Ser Gly Tyr Glu Phe Leu Lys Thr Phe Pro Asp Ile Phe Leu		
	145	150	155 160
25	Gln Pro Tyr Arg Ala Ile Thr Glu Lys Gln Val Val Glu Lys Ala Ile		
	165	170	175
	Leu Ser His Cys His Ala Leu Ala Asn Ala Gly Glu Leu Val Met Val		
30	180	185	190
	Leu Gly Gln Pro Gly Ser Gly Cys Ser Thr Phe Leu Arg Ser Val Thr		
	195	200	205
35	Ser Asp Thr Val His Tyr Lys Arg Val Glu Gly Thr Thr His Tyr Asp		
	210	215	220
	Gly Ile Asp Lys Ala Asp Met Lys Lys Phe Phe Pro Gly Asp Leu Leu		
40	225	230	235 240
	Tyr Ser Gly Glu Asn Asp Val His Phe Pro Ser Leu Thr Thr Ala Glu		
	245	250	255
45	Thr Leu Asp Phe Ala Ala Lys Cys Arg Thr Pro Asn Asn Arg Pro Cys		
	260	265	270
	Asn Leu Thr Arg Gln Glu Tyr Val Ser Arg Glu Arg His Leu Ile Ala		
50	275	280	285
	Thr Ala Phe Gly Leu Thr His Thr Phe Asn Thr Lys Val Gly Asn Asp		
	290	295	300
55	Phe Val Arg Gly Val Ser Gly Gly Glu Arg Lys Arg Val Thr Ile Ser		

EP 1 217 066 A1

	305		310		315		320
5	Glu Gly Phe Ala Thr Arg Pro Thr Ile Ala Cys Trp Asp Asn Ser Thr						
		325		330		335	
10	Arg Gly Leu Asp Ser Ser Thr Ala Phe Glu Phe Val Asn Val Leu Arg						
		340		345		350	
15	Thr Cys Ala Asn Glu Leu Lys Met Thr Ser Phe Val Thr Ala Tyr Gln						
		355		360		365	
20	Ala Ser Glu Lys Ile Tyr Lys Leu Phe Asp Arg Ile Cys Val Leu Tyr						
		370		375		380	
25	Ala Gly Arg Gln Ile Tyr Tyr Gly Pro Ala Asp Lys Ala Lys Gln Tyr						
		385		390		395	
30	Phe Leu Asp Met Gly Phe Asp Cys His Pro Arg Glu Thr Thr Pro Asp						
		405		410		415	
35	Phe Leu Thr Ala Ile Ser Asp Pro Lys Ala Arg Phe Pro Arg Lys Gly						
		420		425		430	
40	Phe Glu Asn Arg Val Pro Arg Thr Pro Asp Glu Phe Glu Gln Met Trp						
		435		440		445	
45	Arg Asn Ser Ser Val Tyr Ala Asp Leu Met Ala Glu Met Glu Ser Tyr						
		450		455		460	
50	Asp Lys Arg Trp Thr Glu Thr Thr Pro Ala Ser Ser Glu Ala Pro Glu						
		465		470		475	
55	Lys Asp Asn Phe Gly Ser Asp Ile Ser Ala Thr Thr Lys His Glu Leu						
		485		490		495	
60	Tyr Arg Gln Ser Ala Val Ala Glu Lys Ser Lys Arg Val Lys Asp Thr						
		500		505		510	
65	Ser Pro Tyr Thr Val Thr Phe Ser Gln Gln Leu Trp Tyr Cys Leu Ala						
		515		520		525	
70	Arg Ser Trp Glu Arg Tyr Ile Asn Asp Pro Ala Tyr Ile Gly Ser Met						
		530		535		540	
75	Ala Phe Ala Phe Leu Phe Gln Ser Leu Ile Ile Gly Ser Ile Phe Tyr						
		545		550		555	
80	Asp Met Lys Leu Asn Thr Val Asp Val Phe Ser Arg Gly Gly Val Leu						

EP 1 217 066 A1

	565	570	575
5	Phe Phe Ser Ile Leu Phe Cys Ala Leu Gln Ser Leu Ser Glu Ile Ala 580 585 590		
10	Asn Met Phe Ser Gln Arg Pro Ile Ile Ala Lys His Arg Ala Ser Ala 595 600 605		
	Leu Tyr His Pro Ala Ala Asp Val Ile Ser Ser Leu Ile Val Asp Leu 610 615 620		
15	Pro Phe Arg Phe Ile Asn Ile Ser Val Phe Ser Ile Val Leu Tyr Phe 625 630 635 640		
20	Leu Thr Asn Leu Lys Arg Thr Ala Gly Gly Phe Trp Thr Tyr Phe Leu 645 650 655		
	Phe Leu Phe Ile Gly Ala Thr Cys Met Ser Ala Phe Phe Arg Ser Leu 660 665 670		
25	Ala Gly Ile Met Pro Asn Val Glu Ser Ala Ser Ala Leu Gly Gly Ile 675 680 685		
30	Gly Val Leu Ala Ile Ala Ile Tyr Thr Gly Tyr Ala Ile Pro Asn Ile 690 695 700		
	Asp Val Gly Trp Trp Phe Arg Trp Ile Ala Tyr Leu Asp Pro Leu Gln 705 710 715 720		
35	Phe Gly Phe Glu Ser Leu Met Ile Asn Glu Phe Lys Ala Arg Gln Phe 725 730 735		
40	Glu Cys Ser Gln Leu Ile Pro Tyr Gly Ser Gly Tyr Asp Asn Tyr Pro 740 745 750		
	Val Ala Asn Lys Ile Cys Pro Val Thr Ser Ala Glu Pro Gly Thr Asp 755 760 765		
45	Tyr Val Asp Gly Ser Thr Tyr Leu Tyr Ile Ser Phe Asn Tyr Lys Thr 770 775 780		
50	Arg Gln Leu Trp Arg Asn Leu Ala Ile Ile Ile Gly Tyr Tyr Ala Phe 785 790 795 800		
	Leu Val Phe Val Asn Ile Val Ala Ser Glu Thr Leu Asn Phe Asn Asp 805 810 815		
55	Leu Lys Gly Glu Tyr Leu Val Phe Arg Arg Gly His Ala Pro Asp Ala		

EP 1 217 066 A1

	820	825	830
5	Val Lys Ala Ala Val Asn Glu Gly Gly Lys Pro Leu Asp Leu Glu Thr 835 840 845		
10	Gly Gln Asp Thr Gln Gly Gly Asp Val Val Lys Glu Ser Pro Asp Asn 850 855 860		
15	Glu Glu Glu Leu Asn Lys Glu Tyr Glu Gly Ile Glu Lys Gly His Asp 865 870 875 880		
20	Ile Phe Ser Trp Arg Asn Leu Asn Tyr Asp Ile Gln Ile Lys Gly Glu 885 890 895		
25	His Arg Arg Leu Leu Asn Gly Val Gln Gly Phe Val Val Pro Gly Lys 900 905 910		
30	Leu Thr Ala Leu Met Gly Glu Ser Gly Ala Gly Lys Thr Thr Leu Leu 915 920 925		
35	Asn Val Leu Ala Gln Arg Val Asp Thr Gly Val Val Thr Gly Asp Met 930 935 940		
40	Leu Val Asn Gly Arg Gly Leu Asp Ser Thr Phe Gln Arg Arg Thr Gly 945 950 955 960		
45	Tyr Val Gln Gln Gln Asp Val His Ile Gly Glu Ser Thr Val Arg Glu 965 970 975		
50	Ala Leu Arg Phe Ser Ala Ala Leu Arg Gln Pro Ala Ser Val Pro Leu 980 985 990		
55	Ser Glu Lys Tyr Glu Tyr Val Glu Ser Val Ile Lys Leu Leu Glu Met 995 1000 1005		
	Glu Ser Tyr Ala Glu Ala Ile Ile Gly Thr Pro Gly Ser Gly Leu Asn 1010 1015 1020		
	Val Glu Gln Arg Lys Arg Ala Thr Ile Gly Val Glu Leu Ala Ala Lys 1025 1030 1035 1040		
	Pro Ala Leu Leu Leu Phe Leu Asp Glu Pro Thr Ser Gly Leu Asp Ser 1045 1050 1055		
	Gln Ser Ala Trp Ser Ile Val Cys Phe Leu Arg Lys Leu Ala Asp Ala 1060 1065 1070		
	Gly Gln Ala Ile Leu Cys Thr Ile His Gln Pro Ser Ala Val Leu Phe		

EP 1 217 066 A1

	1075	1080	1085
5	Asp Gln Phe Asp Arg Leu Leu Leu Leu Gln Lys Gly Gly Lys Thr Val 1090	1095	1100
10	Tyr Phe Gly Asp Ile Gly Glu His Ser Lys Thr Leu Leu Asn Tyr Phe 1105	1110	1115 1120
	Glu Ser His Gly Ala Val His Cys Pro Asp Asp Gly Asn Pro Ala Glu 1125	1130	1135
15	Tyr Ile Leu Asp Val Ile Gly Ala Gly Ala Thr Ala Thr Thr Asn Arg 1140	1145	1150
20	Asp Trp His Glu Val Trp Asn Asn Ser Glu Glu Arg Lys Ala Ile Ser 1155	1160	1165
	Ala Glu Leu Asp Lys Ile Asn Ala Ser Phe Ser Asn Ser Glu Asp Lys 1170	1175	1180
25	Lys Thr Leu Ser Lys Glu Asp Arg Ser Thr Tyr Ala Met Pro Leu Trp 1185	1190	1195 1200
30	Phe Gln Val Lys Met Val Met Thr Arg Asn Phe Gln Ser Tyr Trp Arg 1205	1210	1215
	Glu Pro Ser Ile Leu Met Ser Lys Leu Ala Leu Asp Ile Phe Ala Gly 1220	1225	1230
35	Leu Phe Ile Gly Phe Thr Phe Tyr Asn Gln Gly Leu Gly Val Gln Asn 1235	1240	1245
40	Ile Gln Asn Lys Leu Phe Ala Val Phe Met Ala Thr Val Leu Ala Val 1250	1255	1260
	Pro Leu Ile Asn Gly Leu Gln Pro Lys Phe Ile Glu Leu Arg Asn Val 1265	1270	1275 1280
45	Phe Glu Val Arg Glu Lys Pro Ser Asn Ile Tyr Ser Trp Val Ala Phe 1285	1290	1295
50	Val Phe Ser Ala Ile Ile Val Glu Ile Pro Phe Asn Leu Val Phe Gly 1300	1305	1310
	Thr Leu Phe Phe Leu Cys Trp Phe Tyr Pro Ile Lys Phe Tyr Lys His 1315	1320	1325
55	Ile His His Pro Gly Asp Lys Thr Gly Tyr Ala Trp Leu Leu Tyr Met		

EP 1 217 066 A1

	1330	1335	1340
5	Phe Phe Gln Met Tyr Phe Ser Thr Phe Gly Gln Ala Val Ala Ser Ala 1345	1350	1355 1360
10	Cys Pro Asn Ala Gln Thr Ala Ser Val Val Asn Ser Leu Leu Phe Thr 1365	1370	1375
	Phe Val Ile Thr Phe Asn Gly Val Leu Gln Pro Asn Ser Asn Leu Val 1380	1385	1390
15	Gly Phe Trp His Trp Met His Ser Leu Thr Pro Phe Thr Tyr Leu Ile 1395	1400	1405
20	Glu Gly Leu Leu Ser Asp Leu Val His Gly Leu Pro Val Glu Cys Lys 1410	1415	1420
	Ser His Glu Met Leu Thr Ile Asn Pro Pro Ser Gly Gln Thr Cys Gly 1425	1430	1435 1440
25	Glu Tyr Met Ser Ala Phe Leu Thr Asn Asn Thr Ala Ala Gly Asn Leu 1445	1450	1455
30	Leu Asn Pro Asn Ala Thr Thr Ser Cys Ser Tyr Cys Pro Tyr Gln Thr 1460	1465	1470
	Ala Asp Gln Phe Leu Glu Arg Phe Ser Met Arg Tyr Thr His Arg Trp 1475	1480	1485
35	Arg Asn Leu Gly Ile Phe Val Gly Tyr Val Phe Phe Asn Ile Phe Ala 1490	1495	1500
40	Val Leu Leu Leu Phe Tyr Val Phe Arg Val Met Lys Leu Arg Ser Thr 1505	1510	1515 1520
	Trp Leu Gly Lys Lys Ile Thr Gly Thr Gly 1525	1530	
45			
	<210> 89		
	<211> 1501		
50	<212> PRT		
	<213> Candida albicans		
	<400> 89		
55	Met Ser Asp Ser Lys Met Ser Ser Gln Asp Glu Ser Lys Leu Glu Lys 1	5	10 15

EP 1 217 066 A1

5	Ala Ile Ser Gln Asp Ser Ser Ser Glu Asn His Ser Ile Asn Glu Tyr	20	25	30
	His Gly Phe Asp Ala His Thr Ser Glu Asn Ile Gln Asn Leu Ala Arg	35	40	45
10	Thr Phe Thr His Asp Ser Phe Lys Asp Asp Ser Ser Ala Gly Leu Leu	50	55	60
	Lys Tyr Leu Thr His Met Ser Glu Val Pro Gly Val Asn Pro Tyr Glu	65	70	75
15	His Glu Glu Ile Asn Asn Asp Gln Leu Asn Pro Asp Ser Glu Asn Phe	85	90	95
20	Asn Ala Lys Phe Trp Val Lys Asn Leu Arg Lys Leu Phe Glu Ser Asp	100	105	110
	Pro Glu Tyr Tyr Lys Pro Ser Lys Leu Gly Ile Gly Tyr Arg Asn Leu	115	120	125
25	Arg Ala Tyr Gly Val Ala Asn Asp Ser Asp Tyr Gln Pro Thr Val Thr	130	135	140
30	Asn Ala Leu Trp Lys Leu Ala Thr Glu Gly Phe Arg His Phe Gln Lys	145	150	155
	Asp Asp Asp Ser Arg Tyr Phe Asp Ile Leu Lys Ser Met Asp Ala Ile	165	170	175
35	Met Arg Pro Gly Glu Leu Thr Val Val Leu Gly Arg Pro Gly Ala Gly	180	185	190
40	Cys Ser Thr Leu Leu Lys Thr Ile Ala Val Asn Thr Tyr Gly Phe His	195	200	205
	Ile Gly Lys Glu Ser Gln Ile Thr Tyr Asp Gly Leu Ser Pro His Asp	210	215	220
45	Ile Glu Arg His Tyr Arg Gly Asp Val Ile Tyr Ser Ala Glu Thr Asp	225	230	235
50	Val His Phe Pro His Leu Ser Val Gly Asp Thr Leu Glu Phe Ala Ala	245	250	255
	Arg Leu Arg Thr Pro Gln Asn Arg Gly Glu Gly Ile Asp Arg Glu Thr	260	265	270

EP 1 217 066 A1

5 Tyr Ala Lys His Met Ala Ser Val Tyr Met Ala Thr Tyr Gly Leu Ser
275 280 285

His Thr Arg Asn Thr Asn Val Gly Asn Asp Phe Val Arg Gly Val Ser
290 295 300

10 Gly Gly Glu Arg Lys Arg Val Ser Ile Ala Glu Ala Ser Leu Ser Gly
305 310 315 320

15 Ala Asn Ile Gln Cys Trp Asp Asn Ala Thr Arg Gly Leu Asp Ser Ala
325 330 335

Thr Ala Leu Glu Phe Ile Arg Ala Leu Lys Thr Ser Ala Val Ile Leu
340 345 350

20 Asp Thr Thr Pro Leu Ile Ala Ile Tyr Gln Cys Ser Gln Asp Ala Tyr
355 360 365

25 Asp Leu Phe Asp Lys Val Val Val Leu Tyr Glu Gly Tyr Gln Ile Phe
370 375 380

Phe Gly Lys Ala Thr Lys Ala Lys Glu Tyr Phe Glu Lys Met Gly Trp
385 390 395 400

30 Lys Cys Pro Gln Arg Gln Thr Thr Ala Asp Phe Leu Thr Ser Leu Thr
405 410 415

35 Asn Pro Ala Glu Arg Glu Pro Leu Pro Gly Tyr Glu Asp Lys Val Pro
420 425 430

Arg Thr Ala Gln Glu Phe Glu Thr Tyr Trp Lys Asn Ser Pro Glu Tyr
435 440 445

40 Ala Glu Leu Thr Lys Glu Ile Asp Glu Tyr Phe Val Glu Cys Glu Arg
450 455 460

45 Ser Asn Thr Arg Glu Thr Tyr Arg Glu Ser His Val Ala Lys Gln Ser
465 470 475 480

Asn Asn Thr Arg Pro Ala Ser Pro Tyr Thr Val Ser Phe Phe Met Gln
485 490 495

50 Val Arg Tyr Gly Val Ala Arg Asn Phe Leu Arg Met Lys Gly Asp Pro
500 505 510

55 Ser Ile Pro Ile Phe Ser Val Phe Gly Gln Leu Val Met Gly Leu Ile
515 520 525

EP 1 217 066 A1

5 Leu Ser Ser Val Phe Tyr Asn Leu Ser Gln Thr Thr Gly Ser Phe Tyr
 530 535 540

 Tyr Arg Gly Ala Ala Met Phe Phe Ala Val Leu Phe Asn Ala Phe Ser
 545 550 555 560

 10 Ser Leu Leu Glu Ile Met Ser Leu Phe Glu Ala Arg Pro Ile Val Glu
 565 570 575

 Lys His Lys Lys Tyr Ala Leu Tyr Arg Pro Ser Ala Asp Ala Leu Ala
 15 580 585 590

 Ser Ile Ile Ser Glu Leu Pro Val Lys Leu Ala Met Ser Met Ser Phe
 595 600 605

 20 Asn Phe Val Phe Tyr Phe Met Val Asn Phe Arg Arg Asn Pro Gly Arg
 610 615 620

 Phe Phe Phe Tyr Trp Leu Met Cys Ile Trp Cys Thr Phe Val Met Ser
 25 625 630 635 640

 His Leu Phe Arg Ser Ile Gly Ala Val Ser Thr Ser Ile Ser Gly Ala
 645 650 655

 30 Met Thr Pro Ala Thr Val Leu Leu Leu Ala Met Val Ile Tyr Thr Gly
 660 665 670

 Phe Val Ile Pro Thr Pro Ser Met Leu Gly Trp Ser Arg Trp Ile Asn
 35 675 680 685

 Tyr Ile Asn Pro Val Gly Tyr Val Phe Glu Ser Leu Met Val Asn Glu
 690 695 700

 40 Phe His Gly Arg Glu Phe Gln Cys Ala Gln Tyr Val Pro Ser Gly Pro
 705 710 715 720

 Gly Tyr Glu Asn Ile Ser Arg Ser Asn Gln Val Cys Thr Ala Val Gly
 45 725 730 735

 Ser Val Pro Gly Asn Glu Met Val Ser Gly Thr Asn Tyr Leu Ala Gly
 740 745 750

 50 Ala Tyr Gln Tyr Tyr Asn Ser His Lys Trp Arg Asn Leu Gly Ile Thr
 755 760 765

 Ile Gly Phe Ala Val Phe Phe Leu Ala Ile Tyr Ile Ala Leu Thr Glu
 55 770 775 780

EP 1 217 066 A1

5	Phe Asn Lys Gly Ala Met Gln Lys Gly Glu Ile Val Leu Phe Leu Lys	785	790	795	800
	Gly Ser Leu Lys Lys His Lys Arg Lys Thr Ala Ala Ser Asn Lys Gly		805	810	815
10	Asp Ile Glu Ala Gly Pro Val Ala Gly Lys Leu Asp Tyr Gln Asp Glu		820	825	830
	Ala Glu Ala Val Asn Asn Glu Lys Phe Thr Glu Lys Gly Ser Thr Gly		835	840	845
15	Ser Val Asp Phe Pro Glu Asn Arg Glu Ile Phe Phe Trp Arg Asp Leu		850	855	860
	Thr Tyr Gln Val Lys Ile Lys Lys Glu Asp Arg Val Ile Leu Asp His		865	870	875
20					880
	Val Asp Gly Trp Val Lys Pro Gly Gln Ile Thr Ala Leu Met Gly Ala		885	890	895
25	Ser Gly Ala Gly Lys Thr Thr Leu Leu Asn Cys Leu Ser Glu Arg Val		900	905	910
	Thr Thr Gly Ile Ile Thr Asp Gly Glu Arg Leu Val Asn Gly His Ala		915	920	925
30					
	Leu Asp Ser Ser Phe Gln Arg Ser Ile Gly Tyr Val Gln Gln Gln Asp		930	935	940
35					
	Val His Leu Pro Thr Ser Thr Val Arg Glu Ala Leu Gln Phe Ser Ala		945	950	955
40					960
	Tyr Leu Arg Gln Ser Asn Lys Ile Ser Lys Lys Glu Lys Asp Asp Tyr		965	970	975
45					
	Val Asp Tyr Val Ile Asp Leu Leu Glu Met Thr Asp Tyr Ala Asp Ala		980	985	990
	Leu Val Gly Val Ala Gly Glu Gly Leu Asn Val Glu Gln Arg Lys Arg		995	1000	1005
50					
	Leu Thr Ile Gly Val Glu Leu Val Ala Lys Pro Lys Leu Leu Leu Phe		1010	1015	1020
55					
	Leu Asp Glu Pro Thr Ser Gly Leu Asp Ser Gln Thr Ala Trp Ser Ile		1025	1030	1035
					1040

EP 1 217 066 A1

5	Cys Lys Leu Met Arg Lys Leu Ala Asp His Gly Gln Ala Ile Leu Cys	1045	1050	1055
	Thr Ile His Gln Pro Ser Ala Leu Ile Met Ala Glu Phe Asp Arg Leu	1060	1065	1070
10	Leu Phe Leu Gln Lys Gly Gly Arg Thr Ala Tyr Phe Gly Glu Leu Gly	1075	1080	1085
	Glu Asn Cys Gln Thr Met Ile Asn Tyr Phe Glu Lys Tyr Gly Ala Asp	1090	1095	1100
15	Pro Cys Pro Lys Glu Ala Asn Pro Ala Glu Trp Met Leu Gln Val Val	1105	1110	1115
	Gly Ala Ala Pro Gly Ser His Ala Lys Gln Asp Tyr Phe Glu Val Trp	1125	1130	1135
20	Arg Asn Ser Ser Glu Tyr Gln Ala Val Arg Glu Glu Ile Asn Arg Met	1140	1145	1150
	Glu Ala Glu Leu Ser Lys Leu Pro Arg Asp Asn Asp Pro Glu Ala Leu	1155	1160	1165
30	Leu Lys Tyr Ala Ala Pro Leu Trp Lys Gln Tyr Leu Leu Val Ser Trp	1170	1175	1180
	Arg Thr Ile Val Gln Asp Trp Arg Ser Pro Gly Tyr Ile Tyr Ser Lys	1185	1190	1195
35	Ile Phe Leu Val Val Ser Ala Ala Leu Phe Asn Gly Phe Ser Phe Phe	1205	1210	1215
40	Lys Ala Lys Asn Asn Met Gln Gly Leu Gln Asn Gln Met Phe Ser Val	1220	1225	1230
	Phe Met Phe Phe Ile Pro Phe Asn Thr Leu Val Gln Gln Met Leu Pro	1235	1240	1245
45	Tyr Phe Val Lys Gln Arg Asp Val Tyr Glu Val Arg Glu Ala Pro Ser	1250	1255	1260
50	Arg Thr Phe Ser Trp Phe Ala Phe Ile Ala Gly Gln Ile Thr Ser Glu	1265	1270	1275
	Ile Pro Tyr Gln Val Ala Val Gly Thr Ile Ala Phe Phe Cys Trp Tyr	1285	1290	1295
55				

EP 1 217 066 A1

5 Tyr Pro Leu Gly Leu Tyr Asn Asn Ala Thr Pro Thr Asp Ser Val Asn
1300 1305 1310

Pro Arg Gly Val Leu Met Trp Met Leu Val Thr Ala Phe Tyr Val Tyr
1315 1320 1325

10 Thr Ala Thr Met Gly Gln Leu Cys Met Ser Phe Ser Glu Leu Ala Asp
1330 1335 1340

15 Asn Ala Ala Asn Leu Ala Thr Leu Leu Phe Thr Met Cys Leu Asn Phe
1345 1350 1355 1360

Cys Gly Val Leu Ala Gly Pro Asp Val Leu Pro Gly Phe Trp Ile Phe
1365 1370 1375

20 Met Tyr Arg Cys Asn Pro Phe Thr Tyr Leu Val Gln Ala Met Leu Ser
1380 1385 1390

25 Thr Gly Leu Ala Asn Thr Phe Val Lys Cys Ala Glu Arg Glu Tyr Val
1395 1400 1405

Ser Val Lys Pro Pro Asn Gly Glu Ser Cys Ser Thr Tyr Leu Asp Pro
1410 1415 1420

30 Tyr Ile Lys Phe Ala Gly Gly Tyr Phe Glu Thr Arg Asn Asp Gly Ser
1425 1430 1435 1440

35 Cys Ala Phe Cys Gln Met Ser Ser Thr Asn Thr Phe Leu Lys Ser Val
1445 1450 1455

Asn Ser Leu Tyr Ser Glu Arg Trp Arg Asn Phe Gly Ile Phe Ile Ala
1460 1465 1470

40 Phe Ile Ala Ile Asn Ile Ile Leu Thr Val Ile Phe Tyr Trp Leu Ala
1475 1480 1485

45 Arg Val Pro Lys Gly Asn Arg Glu Lys Lys Asn Lys Lys
1490 1495 1500

50 <210> 90
<211> 1499
<212> PRT
<213> Candida albicans

55 <400> 90

EP 1 217 066 A1

	Met	Ser	Thr	Ala	Asn	Thr	Ser	Leu	Ser	Gln	Gln	Leu	Asp	Glu	Asn	Pro	
	1				5					10					15		
5	Trp	Val	Asp	Ala	Ser	Asp	Asn	Ser	Ser	Val	Gln	Glu	Tyr	Gln	Gly	Phe	
				20					25					30			
10	Asp	Ala	Thr	Ala	Ser	His	Asn	Ile	Gln	Asp	Leu	Ala	Arg	Lys	Leu	Thr	
				35				40					45				
	His	Gly	Ser	Thr	Asn	Gly	Asp	His	His	Ser	Ala	Asn	Asp	Leu	Ala	Arg	
		50					55					60					
15	Tyr	Leu	Ser	His	Met	Ser	Asp	Ile	Pro	Gly	Val	Ser	Pro	Phe	Asn	Gly	
	65					70					75					80	
20	Asn	Ile	Ser	His	Glu	Gln	Leu	Asp	Pro	Asp	Ser	Glu	Asn	Phe	Asn	Ala	
					85					90					95		
	Lys	Tyr	Trp	Val	Lys	Asn	Leu	Lys	Lys	Leu	Phe	Glu	Ser	Asp	Ser	Asp	
				100					105					110			
25	Tyr	Tyr	Lys	Pro	Ser	Lys	Leu	Gly	Val	Ala	Tyr	Arg	Asn	Leu	Arg	Ala	
				115				120					125				
30	Tyr	Gly	Ile	Ala	Asn	Asp	Ser	Asp	Tyr	Gln	Pro	Thr	Val	Thr	Asn	Ala	
		130					135					140					
	Leu	Trp	Lys	Phe	Thr	Thr	Glu	Ala	Ile	Asn	Lys	Leu	Lys	Lys	Pro	Asp	
35	145					150					155					160	
	Asp	Ser	Lys	Tyr	Phe	Asp	Ile	Leu	Lys	Ser	Met	Asp	Ala	Ile	Met	Arg	
					165					170					175		
40	Pro	Gly	Glu	Leu	Thr	Val	Val	Leu	Gly	Arg	Pro	Gly	Ala	Gly	Cys	Ser	
				180					185					190			
	Thr	Leu	Leu	Lys	Thr	Ile	Ala	Val	Asn	Thr	Tyr	Gly	Phe	His	Ile	Gly	
45				195				200					205				
	Lys	Glu	Ser	Gln	Ile	Thr	Tyr	Asp	Gly	Leu	Ser	Pro	His	Asp	Ile	Glu	
		210					215					220					
50	Arg	His	Tyr	Arg	Gly	Asp	Val	Ile	Tyr	Ser	Ala	Glu	Thr	Asp	Val	His	
	225					230					235					240	
	Phe	Pro	His	Leu	Ser	Val	Gly	Asp	Thr	Leu	Glu	Phe	Ala	Ala	Arg	Leu	
55					245					250					255		

EP 1 217 066 A1

	Arg Thr Pro Gln Asn Arg Gly Glu Gly Ile Asp Arg Glu Thr Tyr Ala	
	260	265 270
5	Lys His Met Ala Ser Val Tyr Met Ala Thr Tyr Gly Leu Ser His Thr	
	275	280 285
10	Arg Asn Thr Asn Val Gly Asn Asp Phe Val Arg Gly Val Ser Gly Gly	
	290	295 300
15	Glu Arg Lys Arg Val Ser Ile Ala Glu Ala Ser Leu Ser Gly Ala Asn	
	305	310 315 320
	Ile Gln Cys Trp Asp Asn Ala Thr Arg Gly Leu Asp Ser Ala Thr Ala	
	325	330 335
20	Leu Glu Phe Ile Arg Ala Leu Lys Thr Ser Ala Thr Ile Leu Asp Thr	
	340	345 350
25	Thr Pro Leu Ile Ala Ile Tyr Gln Cys Ser Gln Asp Ala Tyr Glu Leu	
	355	360 365
	Phe Asp Asn Val Val Val Leu Tyr Glu Gly Tyr Gln Ile Phe Phe Gly	
	370	375 380
30	Lys Ala Ser Lys Ala Lys Glu Tyr Phe Glu Asn Met Gly Trp Lys Cys	
	385	390 395 400
35	Pro Gln Arg Gln Thr Thr Ala Asp Phe Leu Thr Ser Leu Thr Asn Pro	
	405	410 415
	Ala Glu Arg Glu Pro Leu Pro Gly Tyr Glu Asp Lys Val Pro Arg Thr	
	420	425 430
40	Ala Gln Glu Phe Glu Thr Phe Trp Lys Asn Ser Pro Glu Tyr Ala Glu	
	435	440 445
45	Leu Thr Lys Glu Ile Asp Glu Tyr Phe Val Glu Cys Glu Arg Ser Asn	
	450	455 460
	Thr Gly Glu Thr Tyr Arg Glu Ser His Val Gly Lys Gln Ser Asn Asn	
	465	470 475 480
50	Thr Arg Pro Ser Ser Pro Tyr Thr Val Ser Phe Phe Met Gln Val Arg	
	485	490 495
55	Tyr Val Ile Ala Arg Asn Phe Leu Arg Met Lys Gly Asp Pro Ser Ile	
	500	505 510

EP 1 217 066 A1

	Pro	Leu	Ile	Ser	Ile	Leu	Ser	Gln	Leu	Val	Met	Gly	Leu	Ile	Leu	Ala	
		515						520					525				
5	Ser	Val	Phe	Phe	Asn	Leu	Arg	Lys	Ser	Thr	Asp	Thr	Phe	Tyr	Phe	Arg	
		530						535					540				
10	Gly	Gly	Ala	Leu	Phe	Phe	Ser	Val	Leu	Phe	Asn	Ala	Phe	Ser	Ser	Leu	
	545						550					555				560	
	Leu	Glu	Ile	Leu	Ser	Leu	Tyr	Glu	Ala	Arg	Pro	Ile	Val	Glu	Lys	His	
					565					570					575		
15	Arg	Lys	Tyr	Ala	Leu	Tyr	Arg	Pro	Ser	Ala	Asp	Ala	Leu	Ala	Ser	Ile	
				580						585					590		
20	Ile	Ser	Glu	Leu	Pro	Val	Lys	Leu	Leu	Met	Thr	Met	Ser	Phe	Asn	Ile	
		595						600					605				
	Val	Tyr	Tyr	Phe	Met	Val	Asn	Leu	Arg	Arg	Thr	Ala	Gly	Asn	Phe	Phe	
	610						615					620					
25	Phe	Tyr	Trp	Leu	Met	Cys	Ala	Ser	Cys	Thr	Leu	Val	Met	Ser	His	Met	
	625					630					635					640	
30	Phe	Arg	Ser	Ile	Gly	Ala	Val	Thr	Thr	Thr	Ile	Ala	Thr	Ala	Met	Ser	
				645						650					655		
	Leu	Ser	Thr	Val	Phe	Leu	Leu	Ala	Met	Ile	Ile	Tyr	Ala	Gly	Phe	Val	
				660					665					670			
35	Leu	Pro	Ile	Pro	Tyr	Ile	Leu	Gly	Trp	Ser	Arg	Trp	Ile	Arg	Tyr	Ile	
		675						680					685				
40	Asn	Pro	Val	Thr	Tyr	Ile	Phe	Glu	Ser	Leu	Met	Val	Asn	Glu	Phe	His	
		690					695						700				
	Gly	Arg	Glu	Phe	Glu	Cys	Gly	Gln	Tyr	Ile	Pro	Ser	Gly	Pro	Gly	Phe	
	705					710					715					720	
45	Glu	Asn	Leu	Pro	Val	Glu	Asn	Lys	Val	Cys	Thr	Thr	Val	Gly	Ser	Thr	
					725					730				735			
50	Pro	Gly	Ser	Thr	Val	Val	Gln	Gly	Thr	Glu	Tyr	Ile	Lys	Leu	Ala	Tyr	
			740					745						750			
	Gln	Phe	Tyr	Ser	Ser	His	Lys	Trp	Arg	Asn	Phe	Gly	Ile	Thr	Val	Ala	
55			755					760					765				

EP 1 217 066 A1

	Phe	Ala	Val	Phe	Phe	Leu	Gly	Val	Tyr	Val	Ala	Leu	Thr	Glu	Phe	Asn
	770						775						780			
5	Lys	Gly	Ala	Ser	Gln	Lys	Gly	Glu	Ile	Val	Leu	Phe	Leu	Lys	Gly	Ser
	785					790					795				800	
10	Leu	Lys	Lys	His	Lys	Arg	Lys	Thr	Ala	Ala	Ser	Asn	Lys	Gly	Asp	Ile
				805					810					815		
	Glu	Ala	Gly	Pro	Val	Ala	Gly	Lys	Leu	Asp	Tyr	Gln	Asp	Glu	Ala	Glu
				820					825					830		
15	Ala	Val	Asn	Asn	Glu	Lys	Phe	Thr	Glu	Lys	Gly	Ser	Thr	Gly	Ser	Val
			835					840					845			
20	Asp	Phe	Pro	Glu	Asn	Arg	Glu	Ile	Phe	Phe	Trp	Arg	Asp	Leu	Thr	Tyr
	850						855						860			
	Gln	Val	Lys	Ile	Lys	Lys	Glu	Asp	Arg	Val	Ile	Leu	Asp	His	Val	Asp
	865					870					875				880	
25	Gly	Trp	Val	Lys	Pro	Gly	Gln	Ile	Thr	Ala	Leu	Met	Gly	Ala	Ser	Gly
					885					890					895	
30	Ala	Gly	Lys	Thr	Thr	Leu	Leu	Asn	Cys	Leu	Ser	Glu	Arg	Val	Thr	Thr
				900					905					910		
	Gly	Ile	Ile	Thr	Asp	Gly	Glu	Arg	Leu	Val	Asn	Gly	His	Ala	Leu	Asp
		915						920					925			
35	Ser	Ser	Phe	Gln	Arg	Ser	Ile	Gly	Tyr	Val	Gln	Gln	Gln	Asp	Val	His
		930					935						940			
40	Leu	Glu	Thr	Thr	Thr	Val	Arg	Glu	Ala	Leu	Gln	Phe	Ser	Ala	Tyr	Leu
	945					950					955				960	
	Arg	Gln	Ser	Asn	Lys	Ile	Ser	Lys	Lys	Glu	Lys	Asp	Asp	Tyr	Val	Asp
					965					970					975	
45	Tyr	Val	Ile	Asp	Leu	Leu	Glu	Met	Thr	Asp	Tyr	Ala	Asp	Ala	Leu	Val
				980					985					990		
50	Gly	Val	Ala	Gly	Glu	Gly	Leu	Asn	Val	Glu	Gln	Arg	Lys	Arg	Leu	Thr
		995						1000						1005		
	Ile	Gly	Val	Glu	Leu	Val	Ala	Lys	Pro	Lys	Leu	Leu	Leu	Phe	Leu	Asp
55		1010						1015						1020		

EP 1 217 066 A1

Glu Pro Thr Ser Gly Leu Asp Ser Gln Thr Ala Trp Ser Ile Cys Lys
 1025 1030 1035 1040
 5
 Leu Met Arg Lys Leu Ala Asp His Gly Gln Ala Ile Leu Cys Thr Ile
 1045 1050 1055
 10
 His Gln Pro Ser Ala Leu Ile Met Ala Glu Phe Asp Lys Leu Leu Phe
 1060 1065 1070
 Leu Gln Lys Gly Gly Arg Thr Ala Tyr Phe Gly Glu Leu Gly Glu Asn
 1075 1080 1085
 15
 Cys Gln Thr Met Ile Asn Tyr Phe Glu Lys Tyr Gly Ala Asp Pro Cys
 1090 1095 1100
 20
 Pro Lys Glu Ala Asn Pro Ala Glu Trp Met Leu Gln Val Val Gly Ala
 1105 1110 1115 1120
 Ala Pro Gly Ser His Ala Lys Gln Asp Tyr Phe Glu Val Trp Arg Asn
 1125 1130 1135
 25
 Ser Ser Glu Tyr Gln Ala Val Arg Glu Glu Ile Asn Arg Met Glu Ala
 1140 1145 1150
 30
 Glu Leu Ser Lys Leu Pro Arg Asp Asn Asp Pro Glu Ala Leu Leu Lys
 1155 1160 1165
 Tyr Ala Ala Pro Leu Trp Lys Gln Tyr Leu Leu Val Ser Trp Arg Thr
 1170 1175 1180
 35
 Ile Val Gln Asp Trp Arg Ser Pro Gly Tyr Ile Tyr Ser Lys Leu Ile
 1185 1190 1195 1200
 40
 Leu Val Ile Ser Ser Ser Leu Phe Ile Gly Phe Ser Phe Phe Lys Ser
 1205 1210 1215
 Lys Asn Asn Leu Gln Gly Leu Gln Ser Gln Met Leu Ala Val Phe Met
 1220 1225 1230
 45
 Phe Phe Val Pro Phe Thr Thr Phe Ile Asp Gln Met Leu Pro Tyr Phe
 1235 1240 1245
 50
 Val Lys His Arg Ala Val Tyr Glu Val Arg Glu Ala Pro Ser Arg Thr
 1250 1255 1260
 55
 Phe Ser Trp Phe Ala Phe Ile Ala Gly Gln Ile Thr Ser Glu Ile Pro
 1265 1270 1275 1280

EP 1 217 066 A1

	Phe Gln Ile Val Val Gly Thr Ile Ser Tyr Phe Cys Trp Tyr Tyr Pro	
	1285	1290 1295
5	Val Gly Leu Tyr Ala Asn Ala Glu Pro Thr Asp Ser Val Asn Ser Arg	
	1300	1305 1310
10	Gly Val Leu Met Trp Met Leu Leu Thr Ala Phe Tyr Val Tyr Thr Ser	
	1315	1320 1325
15	Thr Met Gly Gln Leu Ala Ile Ser Leu Asn Glu Leu Ile Asp Asn Ala	
	1330	1335 1340
	Ala Asn Leu Ala Thr Thr Leu Phe Thr Leu Cys Leu Met Phe Cys Gly	
	1345	1350 1355 1360
20	Val Leu Ala Gly Pro Asn Val Ile Pro Gly Phe Trp Ile Phe Met Tyr	
	1365	1370 1375
25	Arg Cys Asn Pro Phe Thr Tyr Leu Ile Gln Ala Ile Leu Ser Thr Gly	
	1380	1385 1390
	Leu Ala Asn Ala Lys Val Thr Cys Ala Pro Arg Glu Leu Val Thr Leu	
	1395	1400 1405
30	Lys Pro Pro Met Gly Glu Thr Cys Ser Ser Phe Ile Gly Pro Tyr Thr	
	1410	1415 1420
35	Glu Ala Ala Gly Gly Tyr Phe Ser Thr Asn Ser Asp Gly Thr Cys Ser	
	1425	1430 1435 1440
	Val Cys Arg Ile Asp Ser Thr Asn Gln Phe Leu Glu Ser Ile Asn Ala	
	1445	1450 1455
40	Leu Phe Ser Gln Arg Trp Arg Asn Phe Gly Ile Phe Val Ala Phe Ile	
	1460	1465 1470
45	Gly Ile Asn Ile Ile Leu Thr Ile Phe Phe Tyr Trp Leu Ala Arg Val	
	1475	1480 1485
50	Pro Lys Gly Asn Arg Glu Lys Lys Met Lys Lys	
	1490	1495
55	<210> 91	
	<211> 1511	
	<212> PRT	
	<213> Saccharomyces cerevisiae	

EP 1 217 066 A1

<400> 91

5	Met	Pro	Glu	Ala	Lys	Leu	Asn	Asn	Asn	Val	Asn	Asp	Val	Thr	Ser	Tyr	1	5	10	15
10	Ser	Ser	Ala	Ser	Ser	Ser	Thr	Glu	Asn	Ala	Ala	Asp	Leu	His	Asn	Tyr	20	25	30	
15	Asn	Gly	Phe	Asp	Glu	His	Thr	Glu	Ala	Arg	Ile	Gln	Lys	Leu	Ala	Arg	35	40	45	
20	Thr	Leu	Thr	Ala	Gln	Ser	Met	Gln	Asn	Ser	Thr	Gln	Ser	Ala	Pro	Asn	50	55	60	
25	Lys	Ser	Asp	Ala	Gln	Ser	Ile	Phe	Ser	Ser	Gly	Val	Glu	Gly	Val	Asn	65	70	75	80
30	Pro	Ile	Phe	Ser	Asp	Pro	Glu	Ala	Pro	Gly	Tyr	Asp	Pro	Lys	Leu	Asp	85	90	95	
35	Pro	Asn	Ser	Glu	Asn	Phe	Ser	Ser	Ala	Ala	Trp	Val	Lys	Asn	Met	Ala	100	105	110	
40	His	Leu	Ser	Ala	Ala	Asp	Pro	Asp	Phe	Tyr	Lys	Pro	Tyr	Ser	Leu	Gly	115	120	125	
45	Cys	Ala	Trp	Lys	Asn	Leu	Ser	Ala	Ser	Gly	Ala	Ser	Ala	Asp	Val	Ala	130	135	140	
50	Tyr	Gln	Ser	Thr	Val	Val	Asn	Ile	Pro	Tyr	Lys	Ile	Leu	Lys	Ser	Gly	145	150	155	160
55	Leu	Arg	Lys	Phe	Gln	Arg	Ser	Lys	Glu	Thr	Asn	Thr	Phe	Gln	Ile	Leu	165	170	175	
	Lys	Pro	Met	Asp	Gly	Cys	Leu	Asn	Pro	Gly	Glu	Leu	Leu	Val	Val	Leu	180	185	190	
	Gly	Arg	Pro	Gly	Ser	Gly	Cys	Thr	Thr	Leu	Leu	Lys	Ser	Ile	Ser	Ser	195	200	205	
	Asn	Thr	His	Gly	Phe	Asp	Leu	Gly	Ala	Asp	Thr	Lys	Ile	Ser	Tyr	Ser	210	215	220	
	Gly	Tyr	Ser	Gly	Asp	Asp	Ile	Lys	Lys	His	Phe	Arg	Gly	Glu	Val	Val	225	230	235	240
55	Tyr	Asn	Ala	Glu	Ala	Asp	Val	His	Leu	Pro	His	Leu	Thr	Val	Phe	Glu				

EP 1 217 066 A1

	245	250	255
5	Thr Leu Val Thr Val Ala Arg Leu Lys Thr Pro Gln Asn Arg Ile Lys 260 265 270		
10	Gly Val Asp Arg Glu Ser Tyr Ala Asn His Leu Ala Glu Val Ala Met 275 280 285		
	Ala Thr Tyr Gly Leu Ser His Thr Arg Asn Thr Lys Val Gly Asn Asp 290 295 300		
15	Ile Val Arg Gly Val Ser Gly Gly Glu Arg Lys Arg Val Ser Ile Ala 305 310 315 320		
20	Glu Val Ser Ile Cys Gly Ser Lys Phe Gln Cys Trp Asp Asn Ala Thr 325 330 335		
	Arg Gly Leu Asp Ser Ala Thr Ala Leu Glu Phe Ile Arg Ala Leu Lys 340 345 350		
25	Thr Gln Ala Asp Ile Ser Asn Thr Ser Ala Thr Val Ala Ile Tyr Gln 355 360 365		
30	Cys Ser Gln Asp Ala Tyr Asp Leu Phe Asn Lys Val Cys Val Leu Asp 370 375 380		
	Asp Gly Tyr Gln Ile Tyr Tyr Gly Pro Ala Asp Lys Ala Lys Lys Tyr 385 390 395 400		
35	Phe Glu Asp Met Gly Tyr Val Cys Pro Ser Arg Gln Thr Thr Ala Asp 405 410 415		
40	Phe Leu Thr Ser Val Thr Ser Pro Ser Glu Arg Thr Leu Asn Lys Asp 420 425 430		
	Met Leu Lys Lys Gly Ile His Ile Pro Gln Thr Pro Lys Glu Met Asn 435 440 445		
45	Asp Tyr Trp Val Lys Ser Pro Asn Tyr Lys Glu Leu Met Lys Glu Val 450 455 460		
50	Asp Gln Arg Leu Leu Asn Asp Asp Glu Ala Ser Arg Glu Ala Ile Lys 465 470 475 480		
	Glu Ala His Ile Ala Lys Gln Ser Lys Arg Ala Arg Pro Ser Ser Pro 485 490 495		
55	Tyr Thr Val Ser Tyr Met Met Gln Val Lys Tyr Leu Leu Ile Arg Asn		

EP 1 217 066 A1

	500	505	510
5	Met Trp Arg Leu Arg Asn Asn Ile Gly Phe Thr Leu Phe Met Ile Leu 515	520	525
10	Gly Asn Cys Ser Met Ala Leu Ile Leu Gly Ser Met Phe Phe Lys Ile 530	535	540
	Met Lys Lys Gly Asp Thr Ser Thr Phe Tyr Phe Arg Gly Ser Ala Met 545	550	555 560
15	Phe Phe Ala Ile Leu Phe Asn Ala Phe Ser Ser Leu Leu Glu Ile Phe 565	570	575
20	Ser Leu Tyr Glu Ala Arg Pro Ile Thr Glu Lys His Arg Thr Tyr Ser 580	585	590
	Leu Tyr His Pro Ser Ala Asp Ala Phe Ala Ser Val Leu Ser Glu Ile 595	600	605
25	Pro Ser Lys Leu Ile Ile Ala Val Cys Phe Asn Ile Ile Phe Tyr Phe 610	615	620
30	Leu Val Asp Phe Arg Arg Asn Gly Gly Val Phe Phe Phe Tyr Leu Leu 625	630	635 640
	Ile Asn Ile Val Ala Val Phe Ser Met Ser His Leu Phe Arg Cys Val 645	650	655
35	Gly Ser Leu Thr Lys Thr Leu Ser Glu Ala Met Val Pro Ala Ser Met 660	665	670
40	Leu Leu Leu Ala Leu Ser Met Tyr Thr Gly Phe Ala Ile Pro Lys Lys 675	680	685
	Lys Ile Leu Arg Trp Ser Lys Trp Ile Trp Tyr Ile Asn Pro Leu Ala 690	695	700
45	Tyr Leu Phe Glu Ser Leu Leu Ile Asn Glu Phe His Gly Ile Lys Phe 705	710	715 720
50	Pro Cys Ala Glu Tyr Val Pro Arg Gly Pro Ala Tyr Ala Asn Ile Ser 725	730	735
	Ser Thr Glu Ser Val Cys Thr Val Val Gly Ala Val Pro Gly Gln Asp 740	745	750
55	Tyr Val Leu Gly Asp Asp Phe Ile Arg Gly Thr Tyr Gln Tyr Tyr His		

EP 1 217 066 A1

	755	760	765
5	Lys Asp Lys Trp Arg Gly Phe Gly Ile Gly Met Ala Tyr Val Val Phe 770 775 780		
10	Phe Phe Phe Val Tyr Leu Phe Leu Cys Glu Tyr Asn Glu Gly Ala Lys 785 790 795 800		
	Gln Lys Gly Glu Ile Leu Val Phe Pro Arg Ser Ile Val Lys Arg Met 805 810 815		
15	Lys Lys Arg Gly Val Leu Thr Glu Lys Asn Ala Asn Asp Pro Glu Asn 820 825 830		
20	Val Gly Glu Arg Ser Asp Leu Ser Ser Asp Arg Lys Met Leu Gln Glu 835 840 845		
	Ser Ser Glu Glu Glu Ser Asp Thr Tyr Gly Glu Ile Gly Leu Ser Lys 850 855 860		
25	Ser Glu Ala Ile Phe His Trp Arg Asn Leu Cys Tyr Glu Val Gln Ile 865 870 875 880		
30	Lys Ala Glu Thr Arg Arg Ile Leu Asn Asn Val Asp Gly Trp Val Lys 885 890 895		
	Pro Gly Thr Leu Thr Ala Leu Met Gly Ala Ser Gly Ala Gly Lys Thr 900 905 910		
35	Thr Leu Leu Asp Cys Leu Ala Glu Arg Val Thr Met Gly Val Ile Thr 915 920 925		
40	Gly Asp Ile Leu Val Asn Gly Ile Pro Arg Asp Lys Ser Phe Pro Arg 930 935 940		
	Ser Ile Gly Tyr Cys Gln Gln Gln Asp Leu His Leu Lys Thr Ala Thr 945 950 955 960		
45	Val Arg Glu Ser Leu Arg Phe Ser Ala Tyr Leu Arg Gln Pro Ala Glu 965 970 975		
50	Val Ser Ile Glu Glu Lys Asn Arg Tyr Val Glu Glu Val Ile Lys Ile 980 985 990		
	Leu Glu Met Glu Lys Tyr Ala Asp Ala Val Val Gly Val Ala Gly Glu 995 1000 1005		
55	Gly Leu Asn Val Glu Gln Arg Lys Arg Leu Thr Ile Gly Val Glu Leu		

EP 1 217 066 A1

	1010	1015	1020
5	Thr Ala Lys Pro Lys Leu Leu Val Phe Leu Asp Glu Pro Thr Ser Gly 1025	1030	1035 1040
10	Leu Asp Ser Gln Thr Ala Trp Ser Ile Cys Gln Leu Met Lys Lys Leu 1045	1050	1055
	Ala Asn His Gly Gln Ala Ile Leu Cys Thr Ile His Gln Pro Ser Ala 1060	1065	1070
15	Ile Leu Met Gln Glu Phe Asp Arg Leu Leu Phe Met Gln Arg Gly Gly 1075	1080	1085
20	Lys Thr Val Tyr Phe Gly Asp Leu Gly Glu Gly Cys Lys Thr Met Ile 1090	1095	1100
	Asp Tyr Phe Glu Ser His Gly Ala His Lys Cys Pro Ala Asp Ala Asn 1105	1110	1115 1120
25	Pro Ala Glu Trp Met Leu Glu Val Val Gly Ala Ala Pro Gly Ser His 1125	1130	1135
30	Ala Asn Gln Asp Tyr Tyr Glu Val Trp Arg Asn Ser Glu Glu Tyr Arg 1140	1145	1150
	Ala Val Gln Ser Glu Leu Asp Trp Met Glu Arg Glu Leu Pro Lys Lys 1155	1160	1165
35	Gly Ser Ile Thr Ala Ala Glu Asp Lys His Glu Phe Ser Gln Ser Ile 1170	1175	1180
40	Ile Tyr Gln Thr Lys Leu Val Ser Ile Arg Leu Phe Gln Gln Tyr Trp 1185	1190	1195 1200
	Arg Ser Pro Asp Tyr Leu Trp Ser Lys Phe Ile Leu Thr Ile Phe Asn 1205	1210	1215
45	Gln Leu Phe Ile Gly Phe Thr Phe Phe Lys Ala Gly Thr Ser Leu Gln 1220	1225	1230
50	Gly Leu Gln Asn Gln Met Leu Ala Val Phe Met Phe Thr Val Ile Phe 1235	1240	1245
	Asn Pro Ile Leu Gln Gln Tyr Leu Pro Ser Phe Val Gln Gln Arg Asp 1250	1255	1260
55	Leu Tyr Glu Ala Arg Glu Arg Pro Ser Arg Thr Phe Ser Trp Ile Ser		

EP 1 217 066 A1

	1265	1270	1275	1280
5	Phe Ile Phe Ala Gln Ile Phe Val Glu Val Pro Trp Asn Ile Leu Ala	1285	1290	1295
	Gly Thr Ile Ala Tyr Phe Ile Tyr Tyr Tyr Pro Ile Gly Phe Tyr Ser	1300	1305	1310
10	Asn Ala Ser Ala Ala Gly Gln Leu His Glu Arg Gly Ala Leu Phe Trp	1315	1320	1325
	Leu Phe Ser Cys Ala Phe Tyr Val Tyr Val Gly Ser Met Gly Leu Leu	1330	1335	1340
	Val Ile Ser Phe Asn Gln Val Ala Glu Ser Ala Ala Asn Leu Ala Ser	1345	1350	1355
20	Leu Leu Phe Thr Met Ser Leu Ser Phe Cys Gly Val Met Thr Thr Pro	1365	1370	1375
	Ser Ala Met Pro Arg Phe Trp Ile Phe Met Tyr Arg Val Ser Pro Leu	1380	1385	1390
	Thr Tyr Phe Ile Gln Ala Leu Leu Ala Val Gly Val Ala Asn Val Asp	1395	1400	1405
30	Val Lys Cys Ala Asp Tyr Glu Leu Leu Glu Phe Thr Pro Pro Ser Gly	1410	1415	1420
	Met Thr Cys Gly Gln Tyr Met Glu Pro Tyr Leu Gln Leu Ala Lys Thr	1425	1430	1435
	Gly Tyr Leu Thr Asp Glu Asn Ala Thr Asp Thr Cys Ser Phe Cys Gln	1445	1450	1455
40	Ile Ser Thr Thr Asn Asp Tyr Leu Ala Asn Val Asn Ser Phe Tyr Ser	1460	1465	1470
	Glu Arg Trp Arg Asn Tyr Gly Ile Phe Ile Cys Tyr Ile Ala Phe Asn	1475	1480	1485
	Tyr Ile Ala Gly Val Phe Phe Tyr Trp Leu Ala Arg Val Pro Lys Lys	1490	1495	1500
50	Asn Gly Lys Leu Ser Lys Lys	1505	1510	
55				

EP 1 217 066 A1

5 <210> 92
 <211> 1501
 <212> PRT
 <213> *Saccharomyces cerevisiae*

 10 <400> 92
 Met Ser Asn Ile Lys Ser Thr Gln Asp Ser Ser His Asn Ala Val Ala
 1 5 10 15
 Arg Ser Ser Ser Ala Ser Phe Ala Ala Ser Glu Glu Ser Phe Thr Gly
 15 20 25 30
 Ile Thr His Asp Lys Asp Glu Gln Ser Asp Thr Pro Ala Asp Lys Leu
 35 40 45
 20 Thr Lys Met Leu Thr Gly Pro Ala Arg Asp Thr Ala Ser Gln Ile Ser
 50 55 60
 Ala Thr Val Ser Glu Met Ala Pro Asp Val Val Ser Lys Val Glu Ser
 25 65 70 75 80
 Phe Ala Asp Ala Leu Ser Arg His Thr Thr Arg Ser Gly Ala Phe Asn
 85 90 95
 30 Met Asp Ser Asp Ser Asp Asp Gly Phe Asp Ala His Ala Ile Phe Glu
 100 105 110
 Ser Phe Val Arg Asp Ala Asp Glu Gln Gly Ile His Ile Arg Lys Ala
 35 115 120 125
 Gly Val Thr Ile Glu Asp Val Ser Ala Lys Gly Val Asp Ala Ser Ala
 130 135 140
 40 Leu Glu Gly Ala Thr Phe Gly Asn Ile Leu Cys Leu Pro Leu Thr Ile
 145 150 155 160
 Phe Lys Gly Ile Lys Ala Lys Arg His Gln Lys Met Arg Gln Ile Ile
 45 165 170 175
 Ser Asn Val Asn Ala Leu Ala Glu Ala Gly Glu Met Ile Leu Val Leu
 180 185 190
 50 Gly Arg Pro Gly Ala Gly Cys Ser Ser Phe Leu Lys Val Thr Ala Gly
 195 200 205
 Glu Ile Asp Gln Phe Ala Gly Gly Val Ser Gly Glu Val Ala Tyr Asp
 55 210 215 220

EP 1 217 066 A1

5	Gly Ile Pro Gln Glu Glu Met Met Lys Arg Tyr Lys Ala Asp Val Ile	225	230	235	240
	Tyr Asn Gly Glu Leu Asp Val His Phe Pro Tyr Leu Thr Val Lys Gln	245	250	255	
10	Thr Leu Asp Phe Ala Ile Ala Cys Lys Thr Pro Ala Leu Arg Val Asn	260	265	270	
15	Asn Val Ser Lys Lys Glu Tyr Ile Ala Ser Arg Arg Asp Leu Tyr Ala	275	280	285	
	Thr Ile Phe Gly Leu Arg His Thr Tyr Asn Thr Lys Val Gly Asn Asp	290	295	300	
20	Phe Val Arg Gly Val Ser Gly Gly Glu Arg Lys Arg Val Ser Ile Ala	305	310	315	320
25	Glu Ala Leu Ala Ala Lys Gly Ser Ile Tyr Cys Trp Asp Asn Ala Thr	325	330	335	
	Arg Gly Leu Asp Ala Ser Thr Ala Leu Glu Tyr Ala Lys Ala Ile Arg	340	345	350	
30	Ile Met Thr Asn Leu Leu Lys Ser Thr Ala Phe Val Thr Ile Tyr Gln	355	360	365	
35	Ala Ser Glu Asn Ile Tyr Glu Thr Phe Asp Lys Val Thr Val Leu Tyr	370	375	380	
	Ser Gly Lys Gln Ile Tyr Phe Gly Leu Ile His Glu Ala Lys Pro Tyr	385	390	395	400
40	Phe Ala Lys Met Gly Tyr Leu Cys Pro Pro Arg Gln Ala Thr Ala Glu	405	410	415	
45	Phe Leu Thr Ala Leu Thr Asp Pro Asn Gly Phe His Leu Ile Lys Pro	420	425	430	
	Gly Tyr Glu Asn Lys Val Pro Arg Thr Ala Glu Glu Phe Glu Thr Tyr	435	440	445	
50	Trp Leu Asn Ser Pro Glu Phe Ala Gln Met Lys Lys Asp Ile Ala Ala	450	455	460	
55	Tyr Lys Glu Lys Val Asn Thr Glu Lys Thr Lys Glu Val Tyr Asp Glu	465	470	475	480

EP 1 217 066 A1

	Ser Met Ala Gln Glu Lys Ser Lys Tyr Thr Arg Lys Lys Ser Tyr Tyr	
	485	490 495
5	Thr Val Ser Tyr Trp Glu Gln Val Lys Leu Cys Thr Gln Arg Gly Phe	
	500	505 510
10	Gln Arg Ile Tyr Gly Asn Lys Ser Tyr Thr Val Ile Asn Val Cys Ser	
	515	520 525
15	Ala Ile Ile Gln Ser Phe Ile Thr Gly Ser Leu Phe Tyr Asn Thr Pro	
	530	535 540
	Ser Ser Thr Ser Gly Ala Phe Ser Arg Gly Gly Val Leu Tyr Phe Ala	
	545	550 555 560
20	Leu Leu Tyr Tyr Ser Leu Met Gly Leu Ala Asn Ile Ser Phe Glu His	
	565	570 575
25	Arg Pro Ile Leu Gln Lys His Lys Gly Tyr Ser Leu Tyr His Pro Ser	
	580	585 590
	Ala Glu Ala Ile Gly Ser Thr Leu Ala Ser Phe Pro Phe Arg Met Ile	
	595	600 605
30	Gly Leu Thr Cys Phe Phe Ile Ile Leu Phe Phe Leu Ser Gly Leu His	
	610	615 620
35	Arg Thr Ala Gly Ser Phe Phe Thr Ile Tyr Leu Phe Leu Thr Met Cys	
	625	630 635 640
	Ser Glu Ala Ile Asn Gly Leu Phe Glu Met Val Ser Ser Val Cys Asp	
	645	650 655
40	Thr Leu Ser Gln Ala Asn Ser Ile Ser Gly Ile Leu Met Met Ser Ile	
	660	665 670
45	Ser Met Tyr Ser Thr Tyr Met Ile Gln Leu Pro Ser Met His Pro Trp	
	675	680 685
	Phe Lys Trp Ile Ser Tyr Val Leu Pro Ile Arg Tyr Ala Phe Glu Ser	
	690	695 700
50	Met Leu Asn Ala Glu Phe His Gly Arg His Met Asp Cys Ala Asn Thr	
	705	710 715 720
55	Leu Val Pro Ser Gly Gly Asp Tyr Asp Asn Leu Ser Asp Asp Tyr Lys	
	725	730 735

EP 1 217 066 A1

	Val Cys Ala Phe Val Gly Ser Lys Pro Gly Gln Ser Tyr Val Leu Gly	
	740	745 750
5	Asp Asp Tyr Leu Lys Asn Gln Phe Gln Tyr Val Tyr Lys His Thr Trp	
	755	760 765
10	Arg Asn Phe Gly Ile Leu Trp Cys Phe Leu Leu Gly Tyr Val Val Leu	
	770	775 780
	Lys Val Ile Phe Thr Glu Tyr Lys Arg Pro Val Lys Gly Gly Gly Asp	
15	785	790 795 800
	Ala Leu Ile Phe Lys Lys Gly Ser Lys Arg Phe Ile Ala His Ala Asp	
	805	810 815
20	Glu Glu Ser Pro Asp Asn Val Asn Asp Ile Asp Ala Lys Glu Gln Phe	
	820	825 830
	Ser Ser Glu Ser Ser Gly Ala Asn Asp Glu Val Phe Asp Asp Leu Glu	
25	835	840 845
	Ala Lys Gly Val Phe Ile Trp Lys Asp Val Cys Phe Thr Ile Pro Tyr	
	850	855 860
30	Glu Gly Gly Lys Arg Met Leu Leu Asp Asn Val Ser Gly Tyr Cys Ile	
	865	870 875 880
	Pro Gly Thr Met Thr Ala Leu Met Gly Glu Ser Gly Ala Gly Lys Thr	
35	885	890 895
	Thr Leu Leu Asn Thr Leu Ala Gln Arg Asn Val Gly Ile Ile Thr Gly	
	900	905 910
40	Asp Met Leu Val Asn Gly Arg Pro Ile Asp Ala Ser Phe Glu Arg Arg	
	915	920 925
	Thr Gly Tyr Val Gln Gln Gln Asp Ile His Ile Ala Glu Leu Thr Val	
45	930	935 940
	Arg Glu Ser Leu Gln Phe Ser Ala Arg Met Arg Arg Pro Gln His Leu	
	945	950 955 960
50	Pro Asp Ser Glu Lys Met Asp Tyr Val Glu Lys Ile Ile Arg Val Leu	
	965	970 975
	Gly Met Glu Glu Tyr Ala Glu Ala Leu Val Gly Glu Val Gly Cys Gly	
55	980	985 990

EP 1 217 066 A1

	Leu Asn Val Glu Gln Arg Lys Lys Leu Ser Ile Gly Val Glu Leu Val	
	995	1000 1005
5	Ala Lys Pro Asp Leu Leu Leu Phe Leu Asp Glu Pro Thr Ser Gly Leu	
	1010	1015 1020
10	Asp Ser Gln Ser Ser Trp Ala Ile Ile Gln Leu Leu Arg Lys Leu Ser	
	1025	1030 1035 1040
	Lys Ala Gly Gln Ser Ile Leu Cys Thr Ile His Gln Pro Ser Ala Thr	
		1045 1050 1055
15	Leu Phe Glu Glu Phe Asp Arg Leu Leu Leu Arg Lys Gly Gly Gln	
	1060	1065 1070
20	Thr Val Tyr Phe Gly Asp Ile Gly Lys Asn Ser Ala Thr Ile Leu Asn	
	1075	1080 1085
	Tyr Phe Glu Arg Asn Gly Ala Arg Lys Cys Asp Ser Ser Glu Asn Pro	
25	1090	1095 1100
	Ala Glu Tyr Ile Leu Glu Ala Ile Gly Ala Gly Ala Thr Ala Ser Val	
	1105	1110 1115 1120
30	Lys Glu Asp Trp His Glu Lys Trp Leu Asn Ser Val Glu Phe Glu Gln	
	1125	1130 1135
	Thr Lys Glu Lys Val Gln Asp Leu Ile Asn Asp Leu Ser Lys Gln Glu	
35	1140	1145 1150
	Thr Lys Ser Glu Val Gly Asp Lys Pro Ser Lys Tyr Ala Thr Ser Tyr	
	1155	1160 1165
40	Ala Tyr Gln Phe Arg Tyr Val Leu Ile Arg Thr Ser Thr Ser Phe Trp	
	1170	1175 1180
	Arg Ser Leu Asn Tyr Ile Met Ser Lys Met Met Leu Met Leu Val Gly	
45	1185	1190 1195 1200
	Gly Leu Tyr Ile Gly Phe Thr Phe Phe Asn Val Gly Lys Ser Tyr Val	
	1205	1210 1215
50	Gly Leu Gln Asn Ala Met Phe Ala Ala Phe Ile Ser Ile Ile Leu Ser	
	1220	1225 1230
55	Ala Pro Ala Met Asn Gln Ile Gln Gly Arg Ala Ile Ala Ser Arg Glu	
	1235	1240 1245

EP 1 217 066 A1

5 Leu Phe Glu Val Arg Glu Ser Gln Ser Asn Met Phe His Trp Ser Leu
 1250 1255 1260
 Val Leu Ile Thr Gln Tyr Leu Ser Glu Leu Pro Tyr His Leu Phe Phe
 1265 1270 1275 1280
 10 Ser Thr Ile Phe Phe Val Ser Ser Tyr Phe Pro Leu Arg Ile Phe Phe
 1285 1290 1295
 Glu Ala Ser Arg Ser Ala Val Tyr Phe Leu Asn Tyr Cys Ile Met Phe
 1300 1305 1310
 15 Gln Leu Tyr Tyr Val Gly Leu Gly Leu Met Ile Leu Tyr Met Ser Pro
 1315 1320 1325
 20 Asn Leu Pro Ser Ala Asn Val Ile Leu Gly Leu Cys Leu Ser Phe Met
 1330 1335 1340
 Leu Ser Phe Cys Gly Val Thr Gln Pro Val Ser Leu Met Pro Gly Phe
 25 1345 1350 1355 1360
 Trp Thr Phe Met Trp Lys Ala Ser Pro Tyr Thr Tyr Phe Val Gln Asn
 1365 1370 1375
 30 Leu Val Gly Ile Met Leu His Lys Lys Pro Val Val Cys Lys Lys Lys
 1380 1385 1390
 Glu Leu Asn Tyr Phe Asn Pro Pro Asn Gly Ser Thr Cys Gly Glu Tyr
 35 1395 1400 1405
 Met Lys Pro Phe Leu Glu Lys Ala Thr Gly Tyr Ile Glu Asn Pro Asp
 1410 1415 1420
 40 Ala Thr Ser Asp Cys Ala Tyr Cys Ile Tyr Glu Val Gly Asp Asn Tyr
 1425 1430 1435 1440
 Leu Thr His Ile Ser Ser Lys Tyr Ser Tyr Leu Trp Arg Asn Phe Gly
 45 1445 1450 1455
 Ile Phe Trp Ile Tyr Ile Phe Phe Asn Ile Ile Ala Met Val Cys Val
 1460 1465 1470
 50 Tyr Tyr Leu Phe His Val Arg Gln Ser Ser Phe Leu Ser Pro Val Ser
 1475 1480 1485
 55 Ile Leu Asn Lys Ile Lys Asn Ile Arg Lys Lys Lys Gln
 1490 1495 1500

Claims

1. A method for selectively modulating the activity of ABC transporters by influencing the dimerization of the nucleotide binding domains comprising the use of:
 - a) a polypeptide consisting of 5 to 50 amino acids comprising the D loop sequence of an ABC transporter,
 - b) a polypeptide consisting of the D loop sequence of an ABC transporter,
 - c) a peptide mimetic of any of the polypeptides of a) or b), or
 - d) an antisense peptide of the polypeptides of a) or b).
2. A method for selectively modulating the activity of ABC transporters by influencing the dimerization of the nucleotide binding domains according to claim 1 comprising the use of:
 - a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 1 to 43,
 - b) a polypeptide consisting of the amino acid sequence as represented in any of SEQ ID NOs 1 to 43 or a functional homologue thereof,
 - c) a peptide mimetic of any of the polypeptides of a) or b), or
 - d) an antisense peptide of the polypeptides of a) or b).
3. A method for selectively modulating the activity of an ABC transporter according to claim 1 or 2, wherein said ABC transporter belongs to the group of multidrug transporter/P-glycoproteins comprising the use of:
 - a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 1 to 3,
 - b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 1 to 3 or a functional homologue thereof,
 - c) a peptide mimetic of any of the polypeptides of a) or b), or
 - d) an antisense peptide of the peptide of a) or b).
4. A method for selectively modulating the activity of an ABC transporter according to claim 1 or 2, wherein said ABC transporter belongs to the group of the multidrug resistance associated proteins comprising the use of:
 - a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 4 to 15,
 - b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 4 to 15, or a functional homologue thereof,
 - c) a peptide mimetic of any of the polypeptides of a) or b), or
 - d) an antisense peptide of the peptide of a) or b).
5. A method for selectively modulating the activity of an ABC transporter according to claim 1 or 2, wherein said ABC transporter is a bacterial transporter comprising the use of:
 - a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39,
 - b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39, or a functional homologue thereof,
 - c) a peptide mimetic of any of the polypeptides of a) or b), or,
 - d) an antisense peptide of the peptide of a) or b).
6. A method for selectively modulating the activity of an ABC transporter according to claim 1 or 2, wherein said ABC transporter is a fungal transporter comprising the use of:
 - a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 40, 41 or 42,
 - b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 40, 41 or 42, or a functional homologue thereof,
 - c) a peptide mimetic of any of the polypeptides of a) or b), or

d) an antisense peptide of the peptide of a) or b).

7. A method for selectively modulating the activity of an ABC transporter according to claim 1 or 2, wherein said ABC transporter is a protozoal transporter comprising the use of:

- a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 2, 8 or 43,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 2, 8, or 43, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

8. A method according to any of claims 5 to 7 wherein said ABC transporter is involved in bacterial, fungal or protozoal infection of a mammal.

9. A method according to any of claims 5 to 7 wherein said ABC transporter is involved in the induction of resistance to antibiotics or drugs in a mammal.

10. Method for preventing, treating or alleviating diseases associated with the functionality of a human ABC-transporter comprising the use of:

- a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 1 to 36,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 1 to 36, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

11. Method for preventing, treating or alleviating diseases related with bacterial infections comprising the use of:

- a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 29, 37, 38 or 39, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

12. Method for preventing, treating or alleviating diseases related with fungal infections comprising the use of:

- a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 40 to 42,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 40 to 42, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

13. Method for preventing, treating or alleviating diseases related with protozoal infections comprising the use of:

- a) a polypeptide consisting of 5 to 50 amino acids comprising the amino acid sequence represented in any of SEQ ID NOs 2, 8 or 43,
- b) a polypeptide consisting of the amino acid sequence represented in any of SEQ ID NOs 2, 8, or 43, or a functional homologue thereof,
- c) a peptide mimetic of any of the polypeptides of a) or b), or,
- d) an antisense peptide of the peptide of a) or b).

14. A method for identifying compounds which selectively bind to or selectively modulate the properties of ABC transporters, which method comprises:

- a) contacting a compound to be tested with a polypeptide as defined in any of claims 1 to 7, or with a polypeptide corresponding to the D loop of an ABC transporter,
- b) detecting a diminution or inhibition of the activity of said ABC transporter, and,
- c) identifying said compound.

5 15. A method for identifying compounds which selectively bind to or selectively modulate the properties of ABC transporters, which method comprises:

- a) providing a yeast two-hybrid system wherein the nucleotide binding domains NBD1 and NBD2 of an ABC transporter are expressed, or
- 10 b) providing a mammalian expression system wherein the nucleotide binding domains NBD1 and NBD2 of an ABC transporter are expressed, or
- c) providing a bacterial expression system wherein the nucleotide binding domains NBD1 and NBD2 of an ABC transporter are expressed, and,
- 15 d) interacting said compound with the complex formed by the expressed polypeptides as defined in any of a) to c),
- e) inferring from the interaction between said compound and one of the nucleotide binding domains a modulation of the properties of said ABC transporter, and,
- 20 f) identifying said compound.

20 16. An isolated nucleic acid encoding a polypeptide comprising an ABC transporter D-loop as defined in claim 1 or 2.

17. A polypeptide encodable by a nucleic acid of claim 16.

25 18. A cellular host transformed with a nucleic acid encoding at least one nucleotide binding domain of an ABC transporter protein or a nucleic acid comprising a nucleic acid according to claim 16, said nucleic acid in an expressible format for use in a method of claim 15.

30 19. A pharmaceutical composition comprising at least one polypeptide of claim 1 or 2.

20. A compound obtainable by any of the methods of claims 14 or 15.

21. Use of a polypeptide as defined in claim 1 or 2 as a medicament.

35 22. Use of a compound according to claim 20 as a medicament.

23. Use of a polypeptide as defined in claim 17 or a compound obtainable by any of the methods of claims 14 or 15 for preventing, treating or alleviating diseases associated with the functionality of an ABC-transporter.

40 24. Use of a polypeptide as defined in claim 3 or 4 or a compound obtainable by any of the methods of claims 14 or 15 for treatment of cancer.

25. Use of a polypeptide according to claim 24 in combination with chemotherapy.

45 26. Use of a polypeptide as defined in claim 3 or 4 or a compound obtainable by any of the methods of claims 14 or 15 for the preparation of a medicine for treating cancer.

27. Use of a polypeptide as defined in claim 3 or 4 or a compound obtainable by any of the methods of claims 14 or 15 for treating resistance to drugs in a mammal.

50 28. Use of a polypeptide as defined in claim 3 or 4 or a compound obtainable by any of the methods of claims 14 or 15 for the preparation of a medicament for preventing, treating or alleviating diseases associated with drug resistance in a mammal.

55 29. Use of a molecule as defined in claim 5 or a compound obtainable by any of the methods of claims 14 or 15 for preventing, treating or alleviating diseases associated with bacterial infections.

30. Use of a molecule as defined in claim 5 or a compound obtainable by any of the methods of claims 14 or 15 for

the preparation of a medicament for preventing, treating or alleviating diseases associated with bacterial infections.

31. Use of a molecule as defined in claim 5 or a compound obtainable by any of the methods of claims 14 or 15 for treating resistance to antibiotics in a mammal.

32. Use of a molecule as defined in claim 5 or a compound obtainable by any of the methods of claims 14 or 15 for the preparation of a medicament for treating antibiotic resistance in a mammal.

33. Use of a molecule as defined in claim 5 or a compound obtainable by any of the methods of claims 14 or 15 as an anti-bacterial agent.

34. Use of a molecule as defined in claim 6 or a compound obtainable by any of the methods of claims 14 or 15 for preventing, treating or alleviating diseases associated with fungal infections.

35. Use of a molecule as defined in claim 6 or a compound obtainable by any of the methods of claims 14 or 15 for the preparation of a medicament for preventing, treating or alleviating diseases associated with fungal infections.

36. Use of a molecule as defined in claim 6 or a compound obtainable by any of the methods of claims 14 or 15 as a fungicide or anti- fungal agent.

37. Use of a molecule as defined in claim 7 or a compound obtainable by any of the methods of claims 14 or 15 for preventing, treating or alleviating diseases associated with protozoal infections.

38. Use of a molecule as defined in claim 7 or a compound obtainable by any of the methods of claims 14 or 15 for the preparation of a medicament for preventing, treating or alleviating diseases associated with protozoal infections.

39. Use of a molecule as defined in claim 7 or a compound obtainable by any of the methods of claims 14 or 15 as a fungicide or anti- fungal agent.

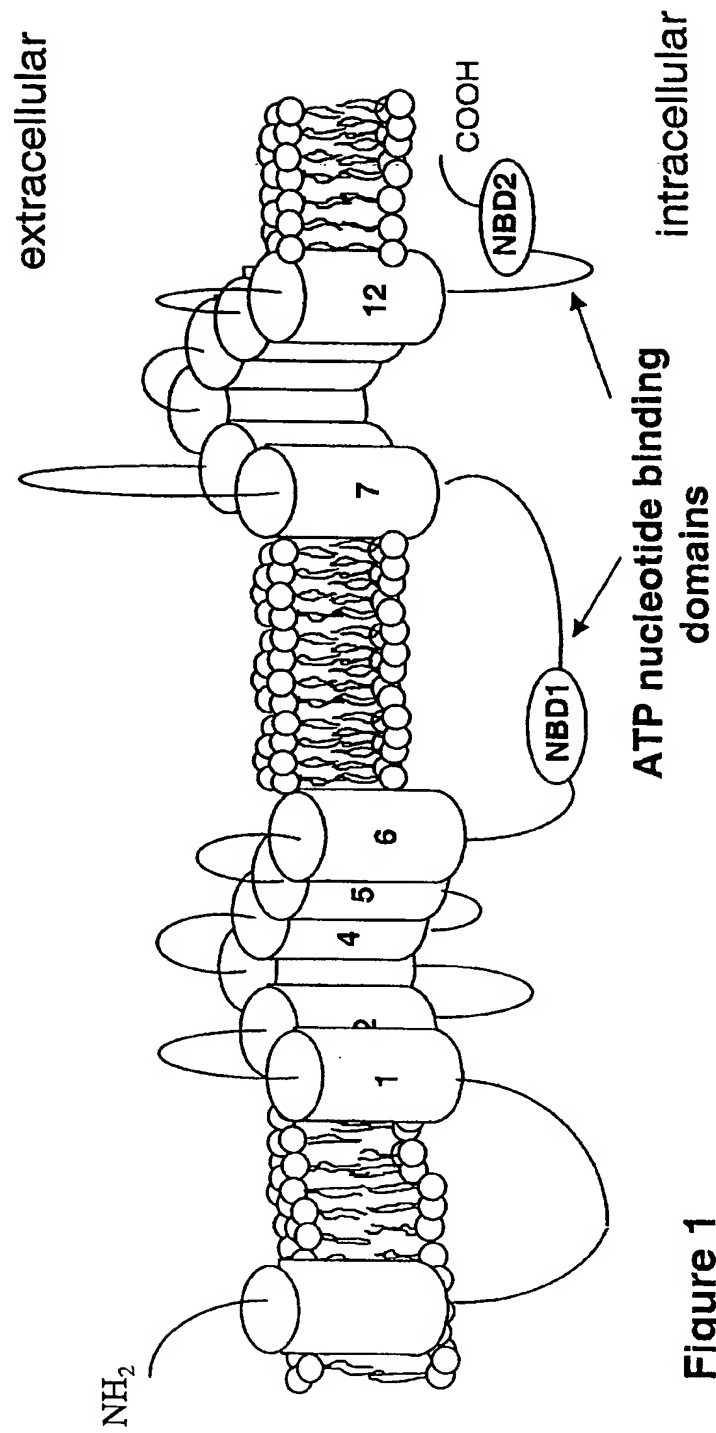


Figure 1

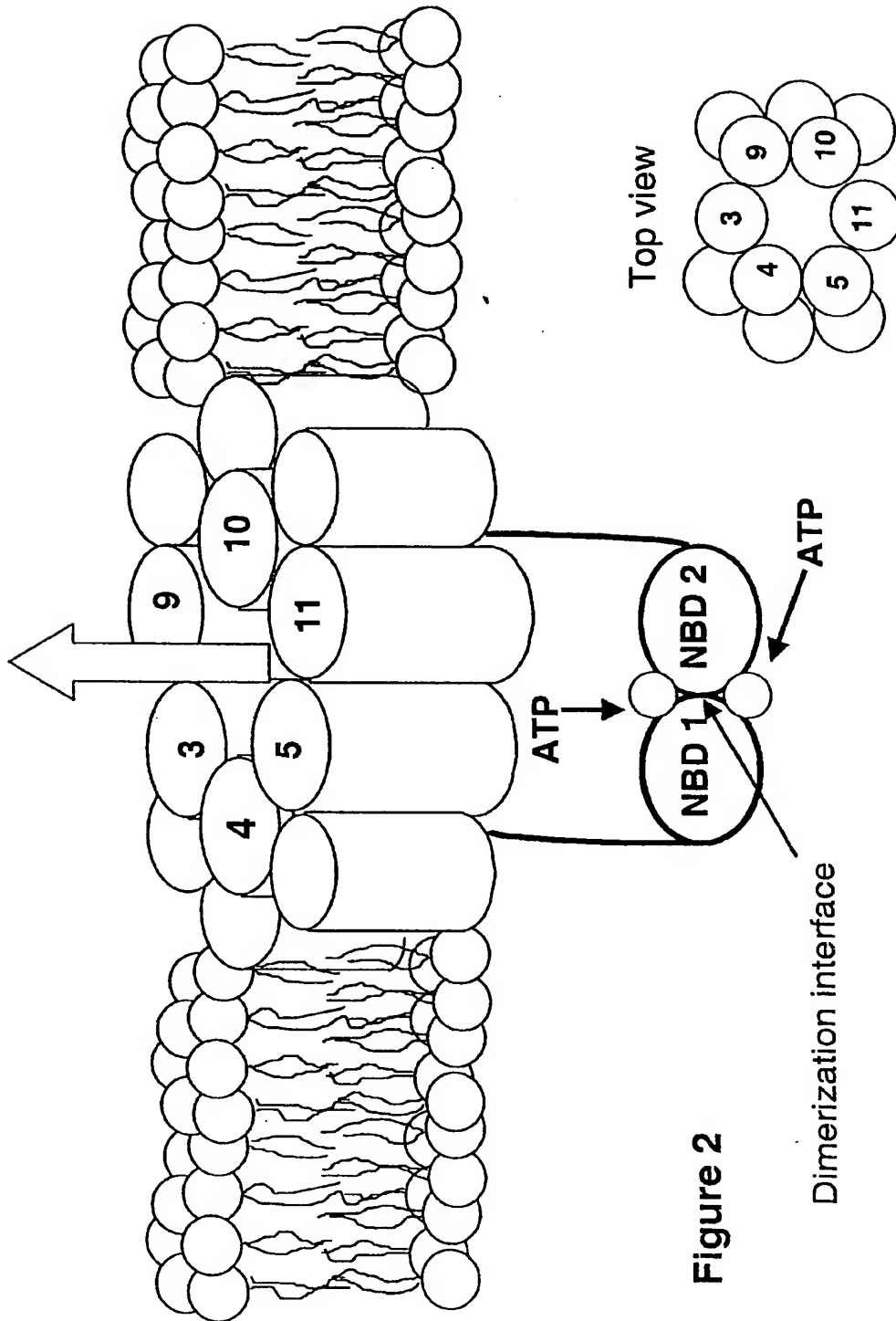


Figure 2

Figure 3 - 1
Figure 3 Human ABC Transporters (examples)

>ABCA1=ABCI

MACWPQLRLLLWKNLTFRRRQTCQLLLEVAWPLFIFLILISVRLSYPPYEQHCHFPNKAMP SAGTLPW
 VQGIICNANNPCFRYPPTGEAPGVVGNFNKSIVARLFS DARRLLLYSQKDTSMKDMRKVLRLTLQOIKKS
 SSNLKLQDFLVDNETFSGFLYHNLSLPKSTVDKMLRADVILHKVFLQGYQLHLTSLCNGSKSEMIQLG
 DQEVSELCLGLPREKLAAAEVRLSRNMDILKPIILRLTNSTSPFPKELAEATKTLHSLGTLAQELFSMR
 SWSDMRQEVFPLTNVNSSSSSTQIYQAVSRIVCGHPGEGGLKIKSLNWYEDNNYKALFGNGTEDEAET
 FYDNSTTPYCNDLMKNLESSPLSRIWKALKPLLVGKILYTPDTPATRVMAEVNKTQELAVFHDLEG
 MWEELSPKIWTTFMENSQEMDLVRMLLDSRDNDHFWEQQLDGLDWAQDIVAFLAKHPEDVQSSNGSVYT
 WREAFNETNQAIRTISRMECVNLNLEPIATEVWLINKSMELLDERKFWAGIVFTGITPGSIELPHHV
 KYKIRMDIDNVERTNKIKDGYWDPGPRADPFEDMRVWGGFAYLQDVVEQAIIRVLTGTTEKKTGVYMQQ
 MPYPCYVDDIFLVRMSRSMPLFMTLAWIYSVAVIIKGIYVEKEARLKETMRIMGLDNSILWF SWFISSL
 IPLLVSAGLLVVILKLGILLPYSDPSVVFVFLSVFAVVTILQCFLISTLFSRANLAAACGGIIYFTLVL
 PYVLVAVWDYVVGFTLKIIFASLLSPVAFGFCGYFALFEEQIGVQWDLNFESPVVEEDGFNLTTVSMM
 LFDFTFLYGVMTWYIEAVFPGQYGI PRPWYFPCTKSYWFGESDEKSHPGSNQKRISEICMEEEPHTLKL
 GVSIGNLVKYRDMKVAVDGLALNFYEGQITSFLGHNGAGKTTTMSILTGLFPPTSGTAYILGKDIRS
 EMSTIRQNLGVCPOHNVLFDMLTVEEHTWYARLKLSEKHVKAEMEOMALDVGLPSSKLKSKTSQSLG
 GMQRKLSVALAFVGSKVVLDEPTAGVDPYSRRGIWELLKRYRQRTIILSTHMDADVLGDRIATII
 SHGKLCCVGSFLKNQLGTGYVLTLVKQDVESLSSCRNSSTVSYLKKEDSVSQSSSDAGLGSDES
 DTLTIDVSAISNLIRKHVSEARLVEDIGHELTYVLPYEAKEGAFVELFHEIDRLSDLGISSYGISET
 TLEEIPLKVAESGVDAETSDGTLPARRNRRAFGDKQSCLRPFTEDDAADPNDSIIDPESRETDLSSGM
 DGKGSYQVKGWKLTOQQFVALLKRLLIARRSRKGFQAQIVLPAVFVCIALVPSLIVPPFGKYP SLELQ
 PWMYNEQYTFVSNDAPEDTGTLELLNALTKDPGFGTRCMEGNPIPDTPCQAGEEWTTPVPQTIMDLF
 QNGNWTMQNPSPACQCSSDKIKKMLPVCPPGAGGLPPORQNTADILQDLTGRNISDYLVKTYVQIIA
 KSLKKNKIWNNEFRYGGFSLGVSNTQALPPSQEVNDATKQMKHKLAKDSSADRPLNSLGRFMTGLDTR
 NNVKVWFNNKGWHAISPLNWINNAILRANLQKGENPSHYGITAFNHPLNLTQQLSEVAPMTTSVDVL
 VSIICVAFMSFVGPASFVVLIOERVS KAKHLQFISGVKPVIIYWL SNFVWDMCNVVPATLVIIIFICFQ
 QKSYVSSNTNLPVLA LLLLYGWSITPLMPASFVFKIPSTAYVVLTSVNLFIGINGSVATFVLELFTDN
 KLNNDILKSVFLIFPHFCLGRGLIDMVKNQAMADALERFGENRFVSPSWDLVGRNLFAMAVEGVV
 FLITVLIQYRRFIRPRPVNAKLSPLNDEDEDVRRERQRI LDGGCQNDILEIKELTKIYRRKRKPAVDRI
 CVGIPPGECFGLLVNGAGKSSSTFKMLTGDTTVTRGDAFLNRNSILSNIHEVHQNMGYCPQFDAITELL
 TGREHVEFFALLRGVPEKEVGKVGWEAIRKLGLVKYGEKYAGNYSNGNKRKLSTAMALIGGPPVFLDE
 PTTGMDPKARRFLWNCALSVVKEGRSVVLTSHSMEECEALCTMAIMVNGRFRCLGSVQHLKNRFGDGY
 TTVVRTAGSNPDLKVPQDFFLAFPGSVPEKHRNMLQYQLPSSLSSARLTPSILSQSKRLHTIEDYSV
 SQTTLQDVFNFAKQSDDDLKDL SLHKNQTVVDVAVLTSPLQDEKVKESYV

>ABCA2=ABC2

MGFLHQLQLLLWKNVTLKRRSPVWLA FEIFIPVLVFFILLGLRQKKPTISVKEVPFYTAAPLTSAGILP
 VMQSLCPDQORDEFGLQYANSTVQTLLERLDRVVEEGLNFDPARPSLGSLEALRQHLEALSAGPGTS
 GSHLDRSTSSFLSDSVARNPQELWRFLTNLNLSPNSTAQALLAARVDPPEVYHLLFGPSSALDSQSL
 HKGQEPWSRLGGNPLFRMEELLLAPALLEQLTCTPGSGELGRILTVPESQKALQGYRDAVCSGQAAAR
 ARRFSGLSAELRNQLDVAKVSQQLGLDAPNGSDSSPQAPPRLQALLGDLDAQKVLQDQVLSALAL
 LLPQGGACTGRTPPGPPASGAGGAANGTGAGAVMGFNATAEAGAPSAALATPDTLQGC SAFVQLWALQ
 PILCGNRTIETPEALRRGNMSSLGFTSKEQRNLGLLVHMTSNPKILYAPAGSEVDRVILKANETPAFV
 GNVTHYAQVWNLISAEIRS FLEQGRLOQLRLWLQYVAELRLHPEALNLSLDELPPALRQDNFSLPSGM
 ALLQQLDTIDNAACGWIQFMSKVSVDIFKGF PDEESIVNYTLNQAYQDNVTVPASVIFQTRKDGSLPH
 VHYKIRQNSSFTEKTNEIRRAYWRPGPNTGGRFYFLYGFVWIQDMMERAIIDTFVGHVVEPGSVVQMF
 PYPCYTRDDFLFVIEHMMPLCMVISWVYSVAMTIQHI VAEKEHRLKEVMKTMGLNNAVHWVAFITGFV
 QLSISVTALTAIKYGOVLHSHSVVILWFLAVYAVATIMFCFLVSVLYSKAKLASACGGIIYFLSYVP
 YMYVAIRREEVAHDKITAF EKCIASLMSTAFGLGSKYFALYEVAGVGIQWHTFSQSPVEGDDFNLLAV
 TMLMVDVAVYGILTWYIEAVHPGMYGLPREWYPLQKSYWLGSGRTEAWESWFWART?RLSVMEEDQA
 CAMESRRFEETRGMEEEPHTLPLVVCVDKLTKVYKDDKKLALNKLNLNLYENQVVSFLGHNGAGKTTM
 SILTGLFPPTSGSATIYGHDIRTEMDEIRKNLGMCPQHNVLFDRLTVEEHLWFYSRLKSMAQEIEIRREM
 DKMIEDLELSNKRHSLVQTLSCGMKRKLSVAIAFVGGSRATILDEPTAGVDPYARRAIWDLILKYKPGR
 TILLSTHMDADLLGDRIATII SHGKLCCGSPFLKGTGYDGYRLTLVKRPAEPGGPQEPGLASSPPG
 RAPLSSCELVQSQFIRKHVASCLLVSDTSTELSYILPSEAKKGAERLFOHLERSLDALHLSFGLM
 DTTLEEVFLKVSEEDQSLENSEADV KESRKDVLPAGEGPASGEGHAGNLARCELTQSQASLQSASSVG
 SARGDEGAGYTDVYGDYRPLFDNPQDPDNVSLQVEAEALSRVQGSRKLDGGWLKVRQPHGLLVKRFH
 CARRNSKALFSQILLPAFFVCVAMTVALSVPEIGDLPPLVLSPSQYHNYTQPRGNFIPIYANERREYRL
 RLSPDASPQQLVSTFRLPSGVGATCVLKS PANGSLGPTLNLSSGESRLAARFFDSMCLESTQGLPLS
 NFVPPPPSPAPSDSPASPEDLQAWNVS LPTAGPEMWTSA PSLRPREVPVRC TCSAQGTGFCSPSSV
 GGHPPQMRVVTGDI LDTITGHNVSEYLLFTSDRFLRHRYGAITFGNVLKSI PASFGTRAPPMVRKIAVR
 RAAQVFYNNKGYHSMPTYLNSLNNAILRANLPKSKGNPAAYGITVTNHPMNTKSASLSLDYLLQGTDDV
 IAIFIIIVAMS FVPASFVVLVAEKSTKAKHLQFVSGCNP IYWLANYVWDMNLNLYLPATCCVILFVFD

Figure 3 - 2

LPAYTSPTNFPVAVLSLFLLYGWSITPIMYPASFWEVPSAYVFLVINLFIGITATVATFLLQLFEHD
 KDLKVVNSYLKSCFLIFPNYNLGHLMEMAYNEYINEYAKIGQFDKMKSPFEWDIVTRGLVAMAVEGV
 VGFLLTIMCQYNFLRRPQRMVPVSTKPEDDVDVASERQVRVLRGDADNDMVKIENLTKVYKSRKIGRILA
 VDRLCLGVRPGECFGLLGUNGAGKTSTFKMLTGDESTTGGAEFVNGHSVLKELLQVQSLGYCPCQDAL
 FDELTAHEHLQYLTRLRGISWKDEARVVKWALEKLELTKYADKPAGTYSGGNKRKLSTALALIGYPAFI
 FLDEPTTGMDFKARRFLWNLLDILIKTGRSVVLTSHSMECEALCTRLAIMVNGRLRCLGSIQHLKNRF
 GDGYMITVTRKSSQSVKDVVRPFNRRNPEAMLKERHHTKVQYQLKSEHISLAQVFSKMEQVSGVLGIED
 YSVSQITLDNVFVNAKKQSDNLEQQETEPSSALQSPLCCLLSLLRPRSAPELRLVADEPEDLDTED
 EGLISFEERAQLSFNTDTLC

>ABCA3=ABC-C

MAVLRQLALLLWKNYTLQKRKVLVTLELFLPLLPFGILWLRLKIQSENVNATIPPQSQIQELPLFF
 TFPFPGDTWELAYIPSHSDAAKTVTETVRRALVINMRVRGFPSEKDFEDYIRYDNCSSSVLAADVFEHP
 FNHSKEPLPLAVKYHLRFSTYTRNVMWTQTSFFLKETEGWHTTSLFLFPNPGPRELTPDGGEPGYI
 REGFLAVQHAVDRAIMEYHADAATRLQFQRLTVTIKRFPPPIADPFLVAIQYQLPLLLLLSFTYTAL
 TIARAVVQEKERRLLKEYMRMGLSSWLHWSAWFLFLFLLLIAASFMTLLFCVKVKNVAVLSRSDPSL
 VLAFLLCFAISTISPSFMVSTFFSKANMAAFAFGFLYFPTYIPYFVAPRYNMTLSQKLCSCLLSNVA
 MAMGAQLIGKFEAKGMGIQWRDLSFVNVDVDFCFQVGLMLLDSVLYGLVWYMEAVFPQGFVGPQP
 WYFFIMPYSWCGKPRVAGKEEDSDPEKALRNEYFEABPEDLVAGIKIKHLSKVFRVGNKDRAAVRDL
 NLNLYEQITVLLGHNGAGKTTLSMLTGLFPPTSGRAYISGYEISQDMVQIRKSLGLCPQHDILFDNL
 TVAEHLVYFAQLKGLSRQKCPPEEVKQMLHIIGLEDKWNRSRFLSGGMRRKLSIGIALIAGSKVLILDE
 PTSGMDAISRRAIWDLQQRKSDRTIVLTTHFMDEADLLGDRIAMAKGELQCCGSSFLKQKYGAGYH
 MTLVKEPCNPNEDISQLVHHVNPATLESSAGAELSFIIPRESTHREFGLFAKLEKKQKELGIASFAS
 ITTMEEVFLRVGKLVDSSMDIQAIQIPALQYQHERRASDWAVDNLCGAMDPDSDGIGALIEBERTAVKL
 NTGLALHCQQFAMFLKKAAYSWEWKMAAQQVLVPLTCVTALLAINYSSELFDPMRLRLTIGEYGR
 VVPFVPGTSQLGQQLSEHLKDALQAEQEPREVLGDLEELIFRASVEGGGPNERCILVAASFDDVGER
 TVNALFNNQAYHSPATALAVVDNLLFKLLCGPHASTVVSNNPQPRSAQAQDQFNEGRKGFIALNL
 LFAMAFLASTFSLAVSERAVQAKHVQFVSGVHVASFWSALLWDLISFLIPSLLLLVLVFKAFDVRFT
 RDGHMADTLLLLLLYGWAIIPMYLNNFFFLGAATAYTRLTIFNLSGIATFLMVTIMRIPAVKLEELS
 KTLDHVFLVLPNHCLGMAVSSFYENYETRRYCTSSSEVAHYCKYNIQYQENFYAWSAPGVGRFVASMA
 ASGCAYLILFLIETNLLQRLRGILCALRRRTLTLEYTRMPVLPEDQDVADETRILAPSPDLSLHTP
 LIITKELSVYEQRVPLAVDRLSLAVQKGEFCGLLGFGNGAGKTTTFKMLTGEESLTSGDAFVGGHRISS
 DVGKVRQRIGYCPQFDALLDHMTGREMLVYARLRGIPERHIGACVENTLRGLLLEPHANKLVRTYSGG
 NKRRLSTGIALIGEPAVIFLDEPSTGMDPVARRLLWDTVARARESGKAIITSHSMECEALCTRLAIM
 VQGGFKCLGSPQHLKSKFGSGYSLRAKVQSEGOQEALEEFKAFVDLTFPGSVLEDEHQGMVHYHLPGRD
 LSWAKVFGILEKAKEKYGVDDYSVSQISLEQVFLSFAHLQPPTAEGR

>ABCA4=ABC-R

MGFVRQIQLLWKNWTLRKRQKIRFVVELVWPLSLFLVLIWLRNANPLYSHHECHFPNKAMPAGMLPW
 LQGFICNVNNPCFQSPTPGESPGIVSNYNNNSILARVYRDFQELLMNAPESQHLGRIWTELHILSQFMDT
 LRTHPIAGRGIRIRDILKDEETLTFLIKNIGLSDSVVYLLINSQVRPEQFAHGVPDLALKDIAACE
 ALLERFIIFSQRRGAKTVRYALCSLSQGTQWIEDTLYANVDFFLFRVLPTLLDSRQGINLRSWGGI
 LSDMSPRIQEFITHRPSMQDQLLWVTRPLMQNGGPETFTKLMGILSDLLCGYPEGGGSRVLSFNWYEDNNY
 KAFGLIDSTRKALIPYISYDRRTTSFCNALIQSLESNPLTKIAWRAAKPLMGKILYTPDSPAARRILKNA
 NSTFELEHVRKLVKAWEEVGPQIWFYFDNSTQMNMRDITLGNPTVKDFLNRQLGEEGITAEAILNPLY
 KGPRESQADDMANFDWRDIFNITDRTLRVLNVQYLECLVLDKFESYNDETQTLQRLSLLEENMFAGV
 FPDYPTWSSLPPIVVKYKIRMDIDVVEKTNKIKDRYWDGPRADPVEDFRYIWGGFAYLQDMVEQGITR
 SQVQAEAPVGIYLLQMPYPCFVDDSFMIILNRCFPIPMVLAWIYSVSMTVKSIVLEKELRLKETLKNQ
 VSNVAVICTWFLDSFSIMSISIFLLTIFIMHGRILHYSDPFIILFLFLAFSTATIMLCFLLSTFFSKAS
 LAAACSGVIYFTLYLPHILCFAWQDRMTAELKAVSLLSPVAFGFGTEYLVRFEQGLQWSNIGNSP
 TEGDEFSPLLSMQMLLDAAACYGLLAWYLDQVFPDYGTPLPWYFLLQESYWLSEGCSTREERALEKT
 EPLTEETEDPEHPEGIHDSEFEREHPGWVPGVCVKNLVKIFEPCCGRPAVDRLNITFYENQITAFLGHN
 AGKTTLSILTGLLPPTSGTVLVGGRIETSLDAVRQSLGMCPOHNLPHHLTVAEHMLFYAQLKGSQ
 EEAQLEMEAMLEDGLHHRKNEEAQDLSCGMQRKLSVAIAFVGDAKVVLDEPTSGVDPYSRRSIWDL
 LKYSRGRTIIMPTTHMDEADHQGDRIAIQAQGRLYCSGTPLFLKNCFGTGLYLTIVLRMKNIQSQRKGS
 EGTCSKSSKGFSTTCPAHVDDLTPQVLDGDVNLMDVVLHHVPEAKLVEICIGQELIFLLPNKNFKHRA
 YASLFRELEETLADLGLSSFGISDTPLEEIFLKVTEDSDSGPLFAGGAQKRENVNPRHPCLGPREKAG
 QTPQDSNVCSFGAPAAHPEGQPPPEPECPCPQLNTGTQLVLQHVQALLVKRFQHTIRSHKDFLAQIVLP
 ATFVPLALMLISIVILPFGYEPALTLHPWIYQQYTFFSMDEPGSEQFTVLADVLLNKPFGNRCLEK
 LPEYPCGNSTPWKTPSVSPNITQLFQKQKWTQVNPSPSCRCSTREKLTMLPECEGAGGLPPQRTQRS
 TEILQDLTDRNISDFLVKTYPALIRSSLSKFWVNEQRYGGISIGGLPVVITGEALVGFLSDLGRIH
 NVSGGPIITREASKEIPDFLKHLETEDNIKVWFNNKGWALVSLFNVAHNAILRASLPKDRSPPEYGITV
 ISQPLNLTKEQLSEITVLTTSVDAVVAICVIFSMSFVPASFVLYLIQERVNKSXHLQFISGVSPPTYWV
 TNFLWIDIMNYSVAGLVVIGFIFGQKAYTSPENLPAVALLLLYGWAVIPMMYPASFLFDVFPSTAYVA
 LSCANLFIGINSSAITFIELEFDNNRLLRFNAVLRLKLLIVFPHFCLGRGLIDLALSQAVTDVYARFGE

Figure 3 - 3

EHSANPFHWDLIGKNLFAMVVEGVVYFLTLVQRHFFLSQWIAEPTKEPIVDEDDVAERQRIITGG
 NKTDLILRLHELTKIYLTSSPAVDRLCVGVPRGECFGLLGNGAGKTTTTFKMLTGDPTVTSGDATVAGK
 SILTNISEVHQMNGYCPQFDAIDELLTGREHLYLVARLRGVPAEEIEKVANWSIKSLGLTVYADCLAGT
 YSGGNKRRLSTAIALIGCPPLVLDEPTTGMDDPQARRMLWNVTISIIRKGRAVVLTSMSMECEALCTR
 LAIMVKGAFRCMGTIOHLKSKFGDGYVTMFKIKSPKDDLLPDLPNVEQFQGNFPGSVQRRHYNMLQF
 QVSSSSLARIFQLLLSHKDSLLIEEYSVTQTTLQVFNFAKQQTESHDLPLHPRAAGASRQAQD

>ABCA7=ABCX

MAFWTQMLLLWKNFMVRRRPVQLLVELLWPLFLFFILVAVRHSHPLEHHECHFENKPLPSAGTVPW
 LQGLICNVNNTCFPQLTPGEEBPGRLSNFNDLSVRLADARTVLGGASAHRTLAGLGLIATLRAARST
 AQPQPTKQSPLEPPMLDVAELTSLRLTESLGLALGQAEPLHSLLEAAEDLAQELLALRSLVELRALL
 QRRPGTSGPLELLSEALCSVRGSPSTVGP SLNWEASDLMELVGQEPESALPDSSLPACSELIGALDS
 HPLSRLLWRRLKPLILGLKLLFAPDTPFTTKLMAQVNRFTBELTLRLDRVREVWMLGPRIFTFMNDSSNV
 AMLQRLLMQDEGRQRPRPGGRDHMEALRSFLDPGSGGYSWQDAHADVGHVLVGTGLGRVTECLSLDKLEA
 APSEAAALVSRAQLLAEHRFWAGVVLGPDSSDPTHEPTDLPDGPVGRVRIKIRMDIDVVRTNKRIRDRF
 WDPGPAADPLTDLRYVWGGFVYLQDLVERAAVRVLSGANPRAGLYLQMPYPCYVDDVFLRVLSRSLPL
 FLTLAWIYSVTLTVKAVVREKETRLRDTMRAMGLSRAVLWLGWFLSCLGPFLLSAALLVLVLKGLDILP
 YSHPGVVFLLFAAFVAVATVTSFLLSAFFSRANLAAACGLAYFSLYLPYVLCVAVRDRLPAGGRVAAS
 LLSVPAFGFCESLALLEEQGEGAQWHNVGTRPTADVFLAQSGLLLDLAALYGLATWYLEAVCPGQY
 GIPFPWNFPFRSYWCGPRPPKSPAPCPTPLDPKVLVEEAPPGLSPGVSVRSLEKRFPGSPQALRGLS
 LDFYQGHITAFGLHNGAGKTTTSLISGLFPFSGGSFALGHVDRSSMAAIRPHLGVCQYVNVLPDMLT
 VDEHVWYFGRKGLSAAVVGPEQDRLLQDVGLVSKQSVQTRHLSGGMQRKLVAIAFVCGSQVVLDEP
 TAGVDPASRRGIWELLKYREGRTLLSTHHLDEAELLGDRVAVVAGGRLLCCGSPFLRLRHLSGSGYFL
 TLVKARLPLTTTNEKADTMEGSDVTDRQEKNGSQSGRVCTPQLLALVQHWVPGARLVEELPHELVLVLP
 YTGADHGSFATLFRDLRLAELRLTGYSIDTSLSEIFLKVVECAADTDMEDGSCGHLCTGIAGLD
 VTLLRLKMPQETALENGEPAGSAPETDQGGSPDAVGRVQGWALTRQQLQALLKRFLLARRSRRLPAQ
 IIVLPALFVGLALVFSLIVPFGHYPALRLSPTMYGAQVSFFSEDA PGDPGRARLLEALQEALEEPV
 QHSSHRFSAPFVPAEVAKVLASGNWTPESPSPACQCSQPGARRLLPDCPAAAGGPPPPQAVTGSSEVVQ
 NLTRGNLSDFLVKTYPRLVQRGLKTKKWNVEVRYGGFSLGGRDPGLPSGQELGRSVEELWALLSPLPGG
 ALDRVLKNTAWAHSLSAQDSLKIWFNNKGNHSMVAFVNRASNAIRLAHLPPGRARHAHSITTLNHLPLN
 LTKQQLFEAALMASSVDVLVSICVVFAMSFVPASFTLVLEERVTRAKHLQMLGGLSPTLYWLGNFLLWD
 MCNVLVPACIVVLIFLAPQORAYVAPANLPAALLLLLLYGSITPLMYPASFFFSVPSTAYVVLTCINL
 FIGINGSMATFVLELFSQDKLQEVSRILKQVFLIFPHFCLGRGLIDMVRNQAMADAFERLGRDQFQSPL
 RWEVVGKNLLAMVIGQPLFLLFTLLQHRSQLLPQPRVRLPLLGEDEEDVARERERVQCATQGDVLV
 LRNLTKVYRQRMPPAVDRLCLGIPPGECFGLLGNGAGKSTFRMTGTDLASRGEAVLAGHSVAREPS
 AAHLSMGYCQSDAIFELLTGREHLELLARLRGVPEAQVQTAGSGLARLGLSWYADRPAITYSGGNKR
 KLATALALVGDPAVVFLDEPTTGMDDPSARRFLWNSLLAVVREGRSVMLTSHSMECEALCSRLAIMVNG
 RFRCLGSPQHLKGRFAAGHTLTLRVPAARSQPAAFVAAEPFPGSELREAHGGRRLRFQLPPGGRCALARV
 FGELAVHGAEHGVEDFSVSTMLEEVLYFSKQDQKDEDETEEQKAGVGVDPAAGLQHPKRVSQFLDDP
 STAETVL

>ABCA8

MRKRKISVVCQQTWALLCKNFLKKWRMKRESLMEWLNSLLLLLLCLYIYPHSHQVNDPSSLLTMDLGRVDT
 FNESRFSVYTPVTNTTQIMNKVASTPFLAGKEVLGLPDEESIKEFTANYPEEIVRVTFNTYSYHLK
 FLLGHGMPAKKEKHDTAHCYETNEDVYCEVSFWKEGFVALQAANAAIIEITTNHSMVEELMSVTGK
 NMKMHSGIFQSGVITDLYLFSCTIISFSSFIYASVNVTRERKRMKALMTMMGLRDSAFWLSWGLLYAGF
 IFIMALFLALVIRSTQFTILSGFMVFLSLFLLYGLSLVALAFLMSILVKKSF LTGLVVFLLTVFWGCLG
 FTSLYRHLPASLEWILSLLSPFAFMGLMAQLLHLDYDLNSNAFPHPSDGSNLIVATNFMALFDTCLYLA
 LAIYFEKILPNEYGHRPPFLFLKSSFWSTQKTDHVALEDEMDADPSFHDSEFQAPPEFQGEAIRIR
 NVTKEYKGDPIEALKDLVFDIYEGQITAILGHSAGKSTLLNLSGLSVPTKGSVTIYNNKLESEMAD
 LENLSKLTGVCPQSNVQFDFLTVRNLRFLAKIKGILPQEVDKEIFLLDEPTAGLDPPFSRHQVWNLKE
 RKTDRVILFSTQFMDEADILADRKFVLSQGLKACGSSFLFKKKWGIYHLSLQLEICVEENITSLVK
 QHIPDAKLSAKSEGLIYTLPLERTNKFPELYKDLSYDGLGIENYGVSMITLNEVFLKLECKSTINES
 DIAILGEVQAEKADDERLVEMEQVLSLNMKRTIGGVALWRQICAIARVRLKLKHERKALLALL
 ILMAGFCPLLVEYTMVKIYQNSYTWE LSPHLYFLAPGQQPHDPLTQLLIINKTGASIDDFIQSVEHQNI
 ALEVDAFGTRNGTDDPSYNGAITVCCNEKNYSFSLACNAKRLNCFVLMDIVSNGLLGMVKPSVHIRTE
 RSTFLENGQDNPIGFLAYIMFWLVTSSCPPIYAMSSIDDYKNRARSQRLISGLSPSAYWFGQALVDVS
 LYFLVVFVLYLSYISNFEDMLLTIIHIIQIPCAVGYSPSLIFMTYVISFIFRKGRKNSGIWSFCFYV
 TVFSVAGFAFSIFESDIPPIFTFLIPPATMIGCLFLSSHLLFSSLFSEERMDVQPFVFLIPLFLHPIIF
 LFTLRKELEWKSGKSMRKDPFPRISPRSDVCQNPEEPEGEDEDVQMERVRTANALNSTNFKDEKPIIA
 SCLRKEYAGKRKCGFSKRKNKIATRNVSFCVRKGEVLGLLGHNGAGKSTSIKVTGTGKTAGQVLLKG
 SGGGDALFELGYCPQENALWPNLTVRQHLEVYAAVKGLRKGDAEVAITRLVDALKLQDLKSPVKTLSE
 GIKRKLFCVLSILGNPSVVLDEPTSTGMDPEGQQQMWQAIATFRNTERGALLTHYMAEAEVCDRVA
 IMVSGRLRCIGSIQHLKSKFGKDYLLKEMVKNLAQVEPLHAEILRLFPQAARQERYSSLMVYKLPVEDV
 QPLAQAFKLEKVKQSFDEEYSLSQSTLEQVFLLELSKEQELGDFEEDFDPSPVKWLLPQEEP

Figure 3 - 4

>ABCB1=MDR1 (multidrug resistance protein1 or P-glycoprotein)
MDLEGRNGGAKKRNFFKLNKSEKDKKKKPTVSVFSMFRYSNWLDKLYMVVGTAAIIHGAGLPLMM
LVFGEMTDIFANAGNLEDLMSNITNRSNDINDTGFFMNLEEDMTRYAYYYSGIGAGVLAAYIQVSWFCL
AAGRQIHKIRKQFFHAIMRQEIGWFDVHDVDELNTRLTDDVSKINEGIGDKIGMFFQSMATFTTGFIVG
FTRGWKLTIVILAI SPVLGLSAAVWAKILSSFTDKELLAYAKAGAVAEVLAIRTVIAFGGQKKELER
YNKNLEEAKRIGIKKAITANISIGAAFLLIYASYALAFWYGTTLVLSGEYSIGQVLTVFSVLIGAFSVG
QASPSIEAFANARGAAVEIFKIIDNKPSIDSYSKSGHKPDNIKGNLEFRNVHFSYPSRKEVKILKGLNL
KVQSGQTVALVGNSSGCGKSTTVQLMQRLYDPTEGMVSVDDQDIRTINVRLREIIGVVSQEPVLPATTI
AENIRYGRNVMTDEIEKAVKEANAYDFIMKLPHKPDTLVGERGAQLSGGQKQRIAIARALVRNPKILL
LDEATSALDTESEAVVQVALDKARKGRTTIVIAHRLSTVRNADVIAGFDDGIVEKGNHDELMKEKGIY
FKLVTMQTAGNEVELENAADESKSEIDALEMSSNDSRSSLIKRSTRRSVRGSAQDRKLTKEALDES
IPPVSWRIMKLNLTENPYFVVGVCALINGGLQPAFAIIFSKIIGVTRIDDPETKRONSNLFSLLFL
ALGIIISFITFFLQGFTEPKAGEILTTRLRYMVFRSMRLQDVSWFDDPKNTTGALTTRLANDAAQVKCAI
GSLRAVITQNIANLTGIIISFIYQWQLTLLLAIVPIIAIAGVVMKMLSGQALKDKKELEGSKGIAT
EATENFRTVSLTQEQQFEHMYAQSLQVPRNSLRKAHIFGITTSFTQAMMYFSYAGCFRFGAYLVAHK
LMSPEDVLLVFSVAVFGAMAVGQVSSFPADYAKAKISAAHIIMIIEKTPIDSYSTEGMLPNTLEGVNT
FGEVVFNYTPRPDIPVLQGLSLEVKKQTLALVGSSSGCGKSTTVQLLERFYDPLAGKVLLDGKEIKRLN
VQWLRAHLGIVSQEPILFDCSIAENIAYGDNSSRVVSQEEIVRAAKEANIHAFTESLPNKYSTKVGDKGT
QLSGGQKQRIAIARALVRQPHILLDDEATSDTESEKVVQEALEDKAREGRTCTVIAHRLSTIQNADLI
VVFQNGRVEHGHGTHQQLAQKGIYFSMVSVQAGTKRQ

>ABCB2=TAP1 (transporter associated with antigen processing)
MAELLASAGSACSWDFPRAPPSFPPPAASRGGLGGTRSFPRHGAESPRPGRDRDGVVRPMASRCRAP
RGCCRLPGASLAWLGTVLLLLADWVLLRTALPRIFSLLVPTALPLLRVWAVGLSRWAVLWLGACGVLR
TVGSKSENAGAQQWLAALKPLAALGLALPGLALFRELISWGAPGSADSTRLLHWGSHPTAFVVSAAAA
LPAAALWHKLGSLWVPGGCGGSGNPRRLGCLGSETRRLSLFLVLVVLSSLGEMAIFFFTGRITDWIL
QDGSADTFTRNLTLMSILTASAVLEFVGDGIYNNMTGHVHSHLQGEVFGAVLRQETEFQONQTNIM
SRVTEDTSTLSDSLSENLSLFLWYLVRGLCLLGLMLWGSVSLTMVTLITLPLLLPKKVGKQWYQLLEV
QVRESLAKSSQVAIEALSAMPTVRSFANEEGEAQKFKREKLQEIKTNLQKEAVAYAVNSWTTISGMLLK
VGILYIGGQLVTSAGVSSGNLVTFLVYQMQFTQAVEVLLSIYPRVQKAVGSSEKIFEYLDRTPRCPSPG
LLTPLHLEGLVQFQDVSFAYPNRPDVLVLQGLTFTLRPEVETALVGPNGSGKSTVAALLQNLQYPTGGQ
LLLDGKPLPQYEHRYLHRQVAAVGQEPQVFGRLQENIAYGLTQKPTMEEITAAAVKSGAHSFISGLPQ
GYDTEVDEAGSQLSGGQRAVALARALIRKPCVLTLDATSALDANSQQLQVEQLLYESPERYSRVLLI
TQHLSLVEQADHILFLEGGAIREGGTHQQLMEKKGCYWAMVQAPADAPE

>ABCB3=TAP2 (transporter associated with antigen processing)
MAELLASAGSACSWDFPRAPPSFPPPAASRGGLGGTRSFPRHGAESPRPGRDRDGVVRPMASRCRAP
RGCCRLPGASLAWLGTVLLLLADWVLLRTALPRIFSLLVPTALPLLRVWAVGLSRWAVLWLGACGVLR
TVGSKSENAGAQQWLAALKPLAALGLALPGLALFRELISWGAPGSADSTRLLHWGSHPTAFVVSAAAA
LPAAALWHKLGSLWVPGGCGGSGNPRRLGCLGSETRRLSLFLVLVVLSSLGEMAIFFFTGRITDWIL
QDGSADTFTRNLTLMSILTASAVLEFVGDGIYNNMTGHVHSHLQGEVFGAVLRQETEFQONQTNIM
SRVTEDTSTLSDSLSENLSLFLWYLVRGLCLLGLMLWGSVSLTMVTLITLPLLLPKKVGKQWYQLLEV
QVRESLAKSSQVAIEALSAMPTVRSFANEEGEAQKFKREKLQEIKTNLQKEAVAYAVNSWTTISGMLLK
VGILYIGGQLVTSAGVSSGNLVTFLVYQMQFTQAVEVLLSIYPRVQKAVGSSEKIFEYLDRTPRCPSPG
LLTPLHLEGLVQFQDVSFAYPNRPDVLVLQGLTFTLRPEVETALVGPNGSGKSTVAALLQNLQYPTGGQ
LLLDGKPLPQYEHRYLHRQVAAVGQEPQVFGRLQENIAYGLTQKPTMEEITAAAVKSGAHSFISGLPQ
GYDTEVDEAGSQLSGGQRAVALARALIRKPCVLTLDATSALDANSQQLQVEQLLYESPERYSRVLLI
TQHLSLVEQADHILFLEGGAIREGGTHQQLMEKKGCYWAMVQAPADAPE

>ABCB4= MDR3= Multidrug Resistance Protein 2 and 3 or P-glycoprotein
3
MDLEAAKNGTAWRPTSAEGDFELGISSKQKRXKTKTKVMIGVLTFRYSDWQDKLFMSLGTIMAIHGS
GLPLMMIVFGEMTDKFDVTAGNFSFPVNFSLSLNPGKILEEEMTRYAYYYSGLGAGVLAAYIQVSWF
TLAAGRQIRKIRKQFFHAILRQEIGWFDINDTTELNTRLTDDISKISEGIGDKVGMFFQAVATFFAGFI
VGFIRGWKLTIVIMAI SPVLGLSAAVWAKILSAFSDKELAAAYAKAGAVAEALGAIRTVIAFGGQKKEL
ERYQKHLENAKEIGIKKAI SANISMGIAPFLLIYASYALAFWYGSTLVISKEYTIGNAMTVFFSILIGAF
SVGQAAPCIDAFANARGAAVIFDIIIDNNPKIDSFSERGHKPDNIKGNLEFNDVHFSYPSRANVKILKG
LNLKVQSGQTVALVGNSSGCGKSTTVQLIQRLYDPDEGTINIDGQDIRNFNVNLYLREIIGVVSQEPVLS
TTIAENICYGRGNVTMDIEKAVKEANAYEFIMKLPHKPDTLVGERGAQLSGGQKQRIAIARALVRNPK
ILLDDEATSALDTESEAEVQALDKAREGRTTIVIAHRLSTVRNADVIAGFEDGVIVEQGSSELMKKE
GVYFKLVNMQTSQSGSIQSEEFELNDEKAATRMANGWSRLFRHSTQKNLKNQMCQKSLDVETDGL
NVPVPSFLKVLKLNKTEWPYFVVGTVCAIANGGLQPAFVIFSEIIAIFGPGDDAVKQKCNIFSLIFL
FLGIIISFTFFLQGFTEPKAGEILTTRLRSMAPKAMLRQDMSWFDHKNSTGALSTRLATDAAQVQAT
GTRLALIAQNIANLTGIIISFIYQWQLTLLLAIVPIIAVSGIVEMKLLAGNAKRDKKELEAGKIAT

Figure 3 - 5

EAIENIRTVVSLTQERKFESMYVEKLYGPRVFSIAIVFGAVALGHASSFA?DYAKAKLSAAHLEFMLFER
 QPLIDSYSSEGLKPKDFEGNITFNEVFNYPTRANVPVLQGLSLEVKKGQTLALVGSSECGKSTVVQLL
 ERFYDPLAGTVLLDQGEAKKLNVQWLRALQGLIVSQEPILFDCSIAENIAYGDNRSRVVSQDEIVSAAKAA
 NIHPPIETLPHKYETRVGDKGTQLSGGQKQRIAIARALIRQPQILLDEATSALDTESEKVVQEALDKA
 REGRTCIVIAHRLSTIQNADLIVVFQNGRVEKHGTHQQLLAQKGIYFSMVSQAGTQNL

>ABCB6

MVTVGNVCEAEGFVGPAWMQDGLSPCFFTLVLPSTRMALGTALVLALPCRRRERPAAGDSLWGAGPR
 ISPYVLQLLATLQALPLAGLAGRVGTARGAPLPSYLLLASVLESAGACGLWLLVVERSQAQRQLAM
 GIWIKFRHSPGLLLLTVAFAENLALVSWNSPQWWARADLGQQVQPSLWVLRVVSGLFVLGLWAP
 GLRPQSYTLQVHEEDQDVERSQVRSAAQSTWRDFGRKLRLLSGYLWPRGSPALQVLVLCGLMGLER
 ALNVLVPIFYRNIVNLLTEKAPWNSLAWITVSYVFLKFLQGGGTGSTGFVSNLRTFLWIRVQQFTSRRV
 ELLIFSHLHELSLRWHLGRRTGEVLRADRGTSSTVGLLSYLVFNVIPTLADIIGIIFYSMFFNAWFG
 LIVFLCMSLYLTITIVTEWRTKFRAMNTQENATRARAVIDSLNPFETVKYNAESYEVEERYEAIKY
 QGLEWSSASLVLLNQTNLVLIGLGLLAGSLLCAYFVTEQKLQVGDYVLFGTYYIQLVYMLNWFGTYYR
 MIQTNFIDMENMFDLLKEETEVDKLPAGPLRFQKGRIEFENVHF SYADGRETLQDVSTVMPGQTLAL
 VGPSPGAGKSTILRLFRFYDISGCIIDGQDISQVTQASLRSHIGVVPQDVTFLNDTIADNIRYGRVT
 AGNDVEAAAQAAGIHDAMAFPEGYRTQVGERGLKLSGGEKQRVAIARTILKAPGITLLDEATSALDT
 SNERAIQASLAKVCANRTTIVVAHRLSTVVNADQILVIKDCGIVERGRHEALLSRGGVYADMWQLQQGQ
 EETSEDTKPQTMER

>ABCB7

MALLAMHSWRWAAAAAFKRRHSAILIRPLVSVSGSGPQWRPHQLGALGTARAYQIPESLKSITWQRL
 KGNSGQFLDAAKALQVWPLIEKRTCWHGHAGGGLHTDPKEGLKDVDTRKIKAMLSYVWPKDRPDLRA
 RVPISLGLGKAGAMNIVVPMFKYAVDSLQMSGNMLNLSAPNTVATMATAVLIGYGVSRAGAAPPN
 EVRNAVFGKVAQNSIRRIAKNVFLHLNLDLGFHLSRQTGALSKAIDRGTRGISFVLSALVFNPLPNHV
 EVMLLVSGVLYYKCCAQLLGNLGLTGTYYTAFTVAVTRWRTRFRLEIDQADNDAGNAIDSLNLETVKY
 FNNERYEAQRYDGLKTYETASLKSTSTLAMLNFGQSAIFSVGLTAIMVLASQGVVAGTLTVGDLVMVN
 GLLFQLSLPLNPLGTVYRTRQALIDMNTLFTLLKVDTOIKDKVMASPLQITPQTATVAFDNVHFYIE
 GQKVLSGISFEVPACKKVAIVGSGSGSKSTIVRLFRFYEPQKGSYLAGQNIQDVLSLESLRRVGVVP
 QDAVLFHNTIYYNLYGNISASPEEVYAVAKLAGLHDAILRMPHGYDTQVGERGLKLSGGEKQRVAIAR
 AILKDPFVILYDEATSSLDISITETILGAMKDVVKHRTSIFIAHRLSTVVDADEITVLDQCKVAERGTH
 HGLLANPHSYSEMWHITQSSRVQNHDPKWEAKKENTISKEERKKLQEEIVNSVKCGCNCSC

>ABCB8

MLVHLFRVIRGGPFPGRLLPPLRFQTSVAVRYSDGYRSSLLRAVAHLSQLWAHLPRAPLAPRWSPS
 AWCWVGALLGPMVLSKHPHLCVLALCEAEAPASSTPHVVGSRFNWKLFWQFLPHLLVLGVAVVLA
 LGAAVLNVQIPLLLGQLVKVAKYTRDHVGSFMTESQNLSTHLLIYGVQGLLTFGYLVLLSHVGERMA
 VDMRRALFSSLLRNITFFDANKTQQLVSRLLTDDQEFKSSFLVLSQGLRSCSQVAGCLVLSMLSTR
 LTLMLVATPALMGVGTLMGSGRLKLSRQCQEHARAMGVADALGNVTRVRLAMEQREEERYGAELE
 ACRCAEELGRGIALFQGLSNIAFNCMLVGLTFIGGSLVAGQQLTGGLDMSFLVASQTVQRSMANLSVL
 FGQVVRGLSAGARVFEYMALNPCIPLSGGCCVPKEQLRGSVTFQNVCFSYPCRPGEVLKDFTLTLP
 KIVALVGQSGGGKTIVASLLERFYDPTAGVVMLDGRDLRTLDPSWLRGQVVGFIHQEPVLFGTTIMENI
 RFGKLEASDEEVYTAAREANAHEFITSFPEGYNTVVGERGTTLSGGQKQRLAIARALIKQPTVLILDEA
 TSALDAESERVVQEALDRASAGRTVLVIAHRLSTVRGAHCIVVMADGRVWEAGTHEELLKKGGLYAELE
 RRQALDAPRTAAPPPKKEPGRSHQHS

>ABCB9

MRLWKAVVVTLAFMSVDICVTTAIYVFSHLDRSLLEDIRHFNIFDSVLDLWAACLYRSCLLLGATIGVA
 KNSALGPRRLRASWLVTITLVCLFVGIIYAMVKLLFSEVRRPIRDPWFALFWWTYISLGASFLWLLS
 TVRPGTQALEPGAATEAEGFPGSGRPPEQASGATLQKLSTYTKPDVAFLVAASFLLIVAALGETFLPY
 YTGRAIDGIVIQKMDQFSTAVVIVCLLAIGSSFAAGIRGGIPTLIFARLNIRLRNCLFRSLVSQETSF
 FDENRTGDLISRLTSDTTMVSVDLSQNIINVFRLNRTVKTGVVVFMSLSWQLSLVTFMGFPPIIMVSN
 YGKYYKRLSKEVQNALARASNTAEETISAMKTVRSFANEEEEEVYLRKLQVYKLNKKEAAAYMYVW
 GSGSVGSVYSGLMQGVGAEEKVFEFIDRQPTMVHDSGLAPDHLEGRVDFENVTFYTRPHTQVLQNV
 FSLSPGKVTALVGPSSGSKSSCVNILENFYPLEGGRVLLDGKPI SAYDHKYLHRVLSLVSQEPVLFARS
 ITDNISYGLPTVPFEMVVEAAQKANAHGFI MELQDGYSTETGEKGAQLSGGQKQRVAMARALVRNPV
 ILDEATSALDAESEYLIQQAITHGNLQKHTVLIIAHRLSTVEHAHLIVVLDKGRVVQQGTHQQLAQGG
 YAKLVQRQMLGLQPAADFTAGHNEPVANGSHKA

>ABCCB10

MRGPPAWPLRLLEPPSPAEPGRLLPVACVWAAASRVPGSLSPFTGLRPARLWAGAPALLWGVCAARRWR
 SGCRGGGPGASRGVLGLARLLGLWARGPGSCRCGAFAGPGAPRLPRARFPGGPAAAWAGDEAWRRGPA
 APPGDKRLRPAAAGLPEARKLLGLAYPERRRLAAAVGFLTMSVVISMSAPFLGKIIDVIYTNPTVDY
 SDNLTIRCLGLSAVFLCGAAANAIRVYLMQTSQQRIVNRLRTSLFSSILRQEVAFDKTRTGELINRLS
 SDTALLGRSVTENLSDGLRAGAQAQSVGISMMFFVSPNLATFVLSVVPVSI IAVIYGRYLRKLKTKVTQD

Figure 3 - 6

SLAQATQLAERIGNVRTVRAFGKEMTEIEKYASKVDHVMQLARKEAVARAGFFGATGLSGNLIVLSVL
YKGLLMGSAHMTVGEISSFLMYAFWVGISIGLSSFYSELMKGLGAGGRLWELLEREPKLPFNEGVL
NEKSFQGALEFKNVHFAYPARPEVPIQDFSLSPSGSVTALVGPSSGSKSTVLSLLRLYNPASGTIS
LDGHDIRQLNPVWLRSKIGTVSQEPILFSCSIAENIAYGADDPSSVTAEIQRVAEVANAVAFIRNFPQ
GFNTVVGKGVLLSGGQKQRIARALALLKNPKILLDEATSDALDAENEYLVQEALDRMDGRITVLVIAH
RLSTIKNANMVAVLDDQKITTEYKHEELLSPNGIYRKLMMNKQSFISA

>ABCB1=SPGP= Sister of P-glycoprotein

MSDSVILRSIKKFGGEENDGFESDKSYNNDKSRQLQDEKKGDVVRVGFQQLFRFSSSTDIWLMFVGSICA
FLHGIAQPGVLLIFGTMTDVFIDYDVELQELQIPGKACVNNITVWNTSSLNQNMNTNGTRCGLLNIESEM
IKFASYAGIYAVAVLITGYIQICFWIAAARQIQKMRKPYFRIRMRMEIGWFDNCNSVGEINTRFSDDDIN
KINDAIADQMALPIQRMSTICGFLGFFRGWKLTLVIIISVSPILIGIGAATIGLSVSKFTDYELKAYAK
AGVVADEVISSMRTVAAFGGEKREVEREYKENVFAQRWGIKRGIVMGFTGFVWCLIFLCYAVAFWYGS
TLVLDGEYTPGTLVQIFLSVIVGALNLGNASPCLEAFATGRAAATSIFETIDRKPIIDCMSEDGYKLD
RIKGEIEFHNVTTFHPSRPEVKILNDLNMVIKPGEMTALVGPSSGAGKSTALQLIQRFYDPCGEMTVTDG
HDIRSLNIQWLRDQIGIVEQEPVLFSTTIAENIRYGREDATMEDIVQAAKEANAYNFIMDLQQQFDTLV
GEGGQMSGGQKQVAVIARALIRNPKILLDMATSDALDNESEAMVQEVLSKIQHGHITIIISVAHRLSTVR
AADTIIIGFEGHTAVERGTHEELLERKGVYPTLVTLQSQGNQALNEEDIKATEDDMLARTFSGSYQDS
LRASIRQRKSKQSLSYLVHEPPLAVVDHKSSTYEEDRKDKDIPVQEEVEPAPVRRILKFSAPWPMYLVGS
VGAANGTITPLVAFILFSGILGTFISI PKKEEQRSQINGVCLLFVAMGCVSLFTQFLQGYAFAKSGELT
KRLRKFGFRAMLGQDIADFDDLRNSPGALTTTLATDASQVQGAAGSQIGMIVNSFTNTVTAMIIAFSPS
WKLSTVLICFFPPLALSGATQTRMLTGFASTRDKQALEMVGQITNEALSNIIRTAVAGIGKERRFIEALETE
LEKPKFTAIQKANTYGCFAFAQCIMFIANSASYRYGGYLISNEGLHFSYVFRVISAVVLSATALGRAF
SYTPSYAKAKISAAFFQLLDROPPIISVYNTAGEKWNDFQCKIDFVDCFTYPSRPSQVNLGLSVSIS
PGQTLAFVGSSSGCKSTSIQLLERFYDQDGKVMIDGHDHKKVNVQFLRSNIGIVSQEPVLFACSIMDN
IKYGDNTKEIPMERVIAAAKQALHDFVMSLPEKYETNVGSQGSQLSRGEKQRIARAIARIVRDPKILL
DEATSDALDTESEKTVQVALDKAREGRTCTIVIAHRLSTIQNADIIAVMAQGVIEKGTHEELMAQKGAYY
KLVTGSPIS

>ABCC1=MRP1= multidrug resistance associated protein 1

MALRGFCSDGSDQLWDWNVTWNTSNPDFTKCFQNTVLVWVPCFYLVACFPFFYFLYLSRHDRGYIQTMP
LNKTKTALGFLWLVWCADLFYSEWERSRGIFLAPVFLVSPITLLGITTLLATFLIQLERRKGVQSSGIM
LTFWLVALCALAFLRSKIMTALKEDAQVLDLFRDITFYVYFSLLLIQLVLSCFSDRSPLFSETIHDNP
CPSSASPLSRITFWWITGLIVRGYRQPLEGSDLSLNKEDTSEQVVPVLVKNWKECAKTRKQPVKVV
YSSQAPQKSSQVDANEVEALIVKSPQKEWNPFLFKVLYKTPGYPFLMSFFPKAHDLMFSGPQI
LKLILKFNVDTKAPDQGYFYTVLLFVTAQLTLVLHGYFHCIFVSGMRIKTAVIGAVYRKALVITNSA
RKSSVTGEIVNLSVDAQRFMDLATYINMIWSAPLQVILALYLLWNLGSPSVLAGVAVMVLMPVNAV
AMKTKTYQVAMSKDNRIKLMNEILNGIKVLYAWELAFKDKVLAIRQEELKVLKKSAYLSAVGTFT
WVCTPFLASVSLKRLRIFLSHELEPDSIERRPVKDGGGTNSITVRNATFTWASDPPTLNGITFSIPE
GALVAVVGQVCGCKSSLLSALLAEMDKVEGHVAIKGSVAYVPPQAWIQNDSLRENILFCQCLEEPYYS
VIQACALLPDLEILPSGDRTEIGKEGVNLSGGQKQKRVSLARAVYSNADITYLFDLPLSAVDAHVGKHIFE
NVIGPKGMLKNKTRILVTHSMSYLPQVDVITVMSGGKISEMGSYQELLARDGAFAEFLRTYASTEQQD
AEENGVTGVSQPGKEAKQMEMLVTDLSAGQLQRLSSSSSYSGDISRHINSTAELOKAEAKKEETWK
LMEADKATGQVFLSVYWDYMAIGLPIFSLISFLMCHVSNALSNYLSLWTDPIVNGTQEHKVR
LSVYGALGISQGIYVFGYSMAVSIIGGILASRCLHVDLLHSILRSPMSPFERTPSGNLVNRFSKELDTVD
SMIPEVIMKFMGSLFENVIGACIVILLATPIAIIIPPLGLIYFFVQRFYVASSRQLKRLSVSRSPVYS
HFNETLLGVSVIRAFEEQERFIHQSDLVKVDENQKAYPSIVANRWLAVRLECVGNCIVLFAALFAVISR
HSLSAGLVGLSVSYSLQVTYTLNWLVRMSSEMETNTIVAVERLKEYSETEKEAPWQIQTAPPSSWPQV
RVEFRNYCLRYREDLDFVLRHINVITINGGEKVGIVGTGAGKSSLTGLFRINESAEGEIIDGINTAKI
GLHDLRFKTIIPQDPVLFSGSLRMNLDPPSQYSDEEVWTSLELAHLKDFVSALPDKLDHECAEGGENL
SVGQRLVCLARALLRKTKILVLDATAAVDLETDLLIQSTIRTTQFEDCTVLTIAHRLNTIMDYTRVIV
LDKGEIQEYGA PSDLLQQRGLFYSMAKDAGLV

>ABCC2=MRP2= Multi Drug Resistance Associated Protein 2

MLEKFCNSTFWNSSFLDSPEADLPLCFEQTVLVWVPLGFLWLLAPWQLLHVYKSRTRKSSSTTKLYLAKQ
VFGVFLILALIELALVLTEDSGQATVPAVRYTNPSLYLGTWLLVLLIYQSRQWCQKNSWFLSLFWIL
SILCGTFQFQTLIRTLQGDNSNLAYSCLFFISYGFQILILIFSAPSENNESSNNPSSIASFLSSITYS
WYDSIILKGYKRPLTLEDVWEVDEEMKTKTLVSKFETHMKRELQKARRALQRRQEKSSSQNSGARLPGL
NKNQSQSQDALVLEDEVEKKKKSGTKKDVPKSWLMKALFKTFYMVLLKSFLKLKLVNDIFTFVSPQLLKL
LISFASDRDYLWIGYLCAILLFTAALIQSFCLQCYFQLCFKLGKVKRTAIMASVYKALTLNLAKE
YTVGETVNVMSVDAQKLMVDVTFMHMLWSSVLQIVLSIFFLWRELGPSVLGAVGVMLVLPINALSTK
SKTIQVKNMKNDKRLKIMNEILSGIKILKYFAWEPSPFRDQVQNLKKELKNLLAFSQLQCVVIFVFQQL
TPVLVSVVTFVSVYVLDVSNILDAQKAFSTITLNFILRPLSMLPMISSLQASVSTERLEKYLGDD
LDTSAIRHDCNFDAKQFSEASTWEHDSATVRDVLNIDMAGQLVAVIGPVGSGKSSLISAMLGEMEN
VHGHITIKGTAYVPPQSWIQNGTIKDNILFGTEFNEKRYQQVLEACALLPDLEMLPGGDALAEIGEKGI
NLSSGQKQRI SLARATYQNLDIYLLDDPLSAVDAHVGKHFVKVLGPNGLLKGKTRLLVTHSMHFLPQV

Figure 3 - 7

DEIVVLNGTIVEKGSYSALLARKGEFAKNLKTFLRHTGPEEEATVHOGSEEEEDDDYGLISSVEEIPED
 AASITMRRENSFRRTLSSRSRNGRHLKSLRNSLKTNRVNSLKEDEELVKQKLIKKEFIETGKVKFSI
 YLEYLQAIGLFSIFFIILAFVMNSVAFIGSNLWLSAWTSDSKI FNSTDYPASQRDMRVGVYALGLAQG
 IFVFIAHFWSAFGVHASNILHKQLLNILRAPMRFFDTPTGRIVNRFAGDISTVDDTL PQSLRSWIT
 CFLGIISTLVMICMATPVFTIIVIPLGIIYVSVMFYVTSRQLRRLDSVTRSPIYSHFSETVSGLPVI
 RAFEHQQRFLLKHNEVRIDTNQKCVFSWITSNRWLALRLLELVGNLTVFFSALMMVIYRDTLSGDTVGVL
 SNALNITQTLNWLVRMTSEIETNIVAVERTTEYTKVENEAPFWTDKRPDPDWPSKGKIQFNNYQVRYRP
 ELDLVLVRGITCDIGSMEKIGVVGRTGAGKSSLTNCLEFRILEAAGGQIITIDGVDIASIGLHDLREKLTII
 PQDPILFSGSLRMLNDPNNYSDEEIKWALELAHLKSFVASLQGLSHEVTEAGGNLSIGQRQLLCLGR
 ALLRKSILVLDATAAVDLETDNLITQTTIQNEFAHCTVITIAHRLHTIMDSKXVMVLDNGKITECGSP
 BELLQIPGPFYFMAKEAGIENVNSTKF

>ABCC3=MRP3= Multi Drug Resistance Associated Protein 3
 MDALCGSGELGSKFWDNSLSVHTENPDLTPCFQNSLLAWVPCIYLWVALPCYLLYLRRHCRGYIILSHL
 SKLKMVLGVLLWCVSADLFPYSFHGLVHGRAPVFFVTPLVVGVTMLLATLLIYERLQGVQSSGVLII
 IFWFLCVCAIVPFRSKILLAKAEGEISDPFRFTTFYIHFALVLSALILACFREKPPPFSAKNVDPNYP
 PETSAGFLSRLFFWFTKMAIYCYRHPLKEDLWSLKEEDRSQMVVQQLLEAWRKQEKQTARHKASAAP
 GKNASGEDEVLLGARPRPRKPSFLKALLATFGSSFLISACFKLIQDLSPINPQLLSILIRFISNPMAP
 SWWGLFVAGLMFLCSMMQSLILQHYHYIFVTGCKFRFTGIMGVIRKALVITNSVKRASTVGEIVNLS
 VDAQRFMDLAPFLNLLWSAPLQIILATYFLWQNLGPSVLGAVFVLLIPLNGAVAVKMRAPQVKQMKL
 KDSRIKLMSEILNGIKVLKLYAWEPSFLKQVEGIRQGEQLLRTAAYLHTTTTFTWMCSPFLVTLITLW
 VVVYVDPNNVLDAAKAFVSLSFNILRLPLNMLPQLISNLTQASVSLKRIQQFLSQEELDPQSVERKTI
 SPGYAITTHSGTFTWAQDLPTLHSLDIQVPGALVAVVGPVCGKSSLSALLGEMEKLEKGVHMKGS
 VAYVPOQAWLQNCITLQENVLFKALNPKRYQQTLEACALLADLEMLPGGDQTEIGEKGINLSGGQRQV
 SLARAVYSDADIFLLDDPLSAVDSHVAKHIFDHVIGPEGVLGKTRVLVTHGISFLPQTDFTIIVLADGQ
 VSEMGYPALLQRNGSPANFLCNYAPDEDOGHLEDSWTALEGAEDKEALLIEDTLNHTDLTDNDPVTY
 VVQKQFMRQLSALSSDGEQGRVPRRHLPSEKQVTEAKADGALTQEEKAAIGTVELSVFWDYAKAV
 GLCTFLAICLLYVYGSAAGANVWLSAWTNDAMADSRQNTSLRLGVYALGILQGFVLVLAAMAMAA
 GGIQTAARLHQAALHNKIRSPQSFDDTTPSGRILNCFSKDIYVDEVLAPVILMLNLSFFNAISTLVVI
 MASTPLFTTVILPLAVLYTLVQRFYAATSRQLKRLESVSRSPIYSHFSETVTGASVIRAYNRSRDFEII
 SDTKVDANQRSCYPIIISNRWLSIGVEFVGNVVLFAALFAVIGRSSNLNPLGVLSVSYSLQVTFALNW
 MIRMSDLHLSNIVAVERVKEYSKTEAPVWVVEGSRPEGWPRGEVEFRNYSVRYRPGDLVLRLDSL
 HVHGGKVGIVGRTGAGKSSMTLCLFRILEAAKGEIRIDGLNVADIGLHDLRSQTLTIIPQDPILFSGTL
 RMNLDPPGSGSYSEEDIWALELSHLHTFVSSQPAGLDQCSEGGENLSVGQRQLVCLARALLRKSRIILVL
 DEATAAIDLETDNLIQATIRTDCTVLTIAHRLNTIMDYTRVLVLDKGVVAEFDSPANLIAARGIFY
 GMARADGLA

>ABCC4= MRP4= Multidrug Resistance Associated Protein 4
 MLPVYQEVKNPILQDANICSRVFFWNLNPLFKIGHKRRLLEEDDMYSVLPEDRSQHLGEELQGFWDKEVL
 RAENDAQKPSLTRAIIKCYKSYLVGLIFTLIEESAKVIQPIFLGKIINYFENYDPMDSVALNTAYAYA
 TVLTFTCTLILAILHLYFYHVQCAGMRLRVAMCHMIYRKALRLSNMAMGKTTTGQIVNLLSNDVNKFDQ
 VTVFLFHLWAGPLQAIAVTALLWMEIGISCLAGMAVLIILLPLQSCFGKLFSSLSRKTATFTDARITM
 NEVITGIRIIMYAWEKSFNLTITNLKKEISKILRSSCLRGMNLASFSAKIIIVFVTFTTYVLGVS
 ITASRVFVAVTLYGAVRLTVLTFPSPAIERVSEAIVSIRRIQTFLLDDEISQRNRQLPSDGKKMVHVQD
 PFAFWDKASETPTLQGLSFTVRPGELLAVVGPVGAGKSSLLSAVLGELAPSEGLSVHGRIAYVSQGPW
 VPSGTLRSNIFLGKKEKERYEKVAKACALKKDLQLEDGDLTVIGDRGTTLSGGQKARVNLARAVYQD
 ADIYLLDDPLSAVDAEVSRLHFLCICQILHEKITILVTHQLQYLKAASQILILKDGKMWQKGTYTEFL
 KSGIDFGSLLKKDNEEQPPVPGTPTLRNRTFSESSVWSQSSRPSLKDGALESQDTEENVPTLSEEN
 RSEGVGFQAYKNYFRAGAHWIVFIFLILLNTAAQVAVVLQDWLWSYANKQSMNLNVTNNGGNGVTEKL
 DLNWLGLIYSGTLVATVLFGLIARSLVYVVLVNSQTILHNKMFESILKAPVLFDRNPIGRILNRFSD
 IGHLDLPLTLFLDFIQTLLQVGVVSVAVAVIPWIAIPLVPLGIIFIFLRRYFLETSRDVKRLESTTR
 SPVFSHLLSSSLQGLWTIRAYKAEERCQELFDAHQDLHSEAWFLFLTTSRWFAVRLDAICAMFVIVAFG
 SLILAKTLDAQVGLALSALYALTLGMFQWCVQSAEVENMMISVERVIEYTDLEKEAPWBYQKRPPPAW
 PHEGVIIIFDNVNFMYSPGGPLVLKHLTALIKSQEKVIGVGTGAGKSSLSALFRLSEPEGKIWDKIL
 TTEIGLHDLRKKMSIIPQEPVLTGTMRKNLDPFKEHTDEELWNLQEVQLKETIEDLPKMDTELAES
 GSNFVSGQRQLVCLARAILRKNQILIDEATANVDPRTELIQKKIREKFAHCTVLTIAHRLNTIIDSD
 KIMVLDSCRLEKEYDEPVYLLQNKESLFYKMQQLGKAEAAALTETAKQVYFKRNPHTIGHTDHMTNTS
 NGQPSTLTIFETAL

>ABCC5= MRP5= Multidrug Resistance Associated Protein 5
 MKDIDIGKEYIIPSGYRSVRERTSTSGTHRDREDSKFRRTPLQCDALETAARAEGLSLDASMHSQ
 RILDEEHKPKYHHLGALKPIRTTSKHQHPVDNAGLFSCMTFSWLSLARVAHKKGELSMEDVWSLSK
 HESSDVNCRRLERLWQELNEVGPDASLRVVWIFCRTLILSVCLMITQLAGFSGPAFMVKHLLLEY
 TQATESNLQYSLLLVLGLLLEIVRSWSLALTWALNYRTGVRLRGAILTMAFKKILKLNKEKSLGEL
 INICSDGQRMFEEAAVGSLLAGGPVVAAILGMIYNVILGPTGFLGSAVFILFYPAMMFASRLTAYFRR
 KCVAATDERVQKMNEVLTYYIKFIKMYAWWKAQSQVQKIREEERRILEKAGYFQGITVGVAPIVVVIAS

Figure 3 - 8

VVTF SVHMTLGFDLTAAQAFVTVTFNSMTFALKVTPFVSXSLSEASVAVDRFKSLFLMEEVHMIKKNP
 ASPHIKIEKNATLAWDSHSSSIQNSPKLTPEMKKDKRASRGKKEKVRQLQRTHEQAVLAEQKGHLLLD
 SDERPSPREEEGKHILHGLRLQRTLSIDLEIQEGKLVGICGSVSGKTSLSAILGQMTLLEGSIAI
 SGTFAVVAQAWILNATLRDNLFGKEYDEBRYNSVLNSCCLRPDLAILPSSDLTEIGERGANLGGQR
 QRI SLARALYSRDSIYILDDPLSALDAHVGNIHFNSAIRKHLKSKTVLFTVHQLQYLVDCEVI FMKKG
 CITERGTHEELMNLNGDYATIFNNLLGETPPVEINSRKETSGSQKKSQDKGPKTGSVKKEKAVKPEEG
 QLVQLEEKQGSVPWSVYGVYIQAAGGPLAFVLVIMALFMLNVGSTAFSTWWSYWIQKQSGNMTTVTRGN
 ETSVSDSMKDNPHMQYASIVALSMAVMLILKAIKGVVFKGTLRASSRLHDELFRILRSPMKFFDFTT
 PTGRILNRFKSKMDDEVDRPLPFAEMFIQNVILVFFCVGMIAGVFPWFVLVAVGVLVILFSLVHIVSRVL
 IRELKRLDNITQSPFLSHITSSIQGLATIHAYNKQGEFLHRYQELDDNQAPFFLFTCAMRWLAVRLDL
 ISIALITTTGLMIVLMHGQIPPAYAGLAISYAVQLTGLFQFTVRLASETEARFTSVERINHYIKTSLSE
 APARIKNKAPSDWPQGEVTFENAEMRYRENPLVLKVSFTIKPKEKIGIVGRTSGSKSLGMALFR
 LVELSGGCKIDGVRISDIGLADLRSLKSIIPQEPVLFSGTVRSNLDPPNQYTEDQIWDALERTHMKEC
 IAQLPLKLESEVMENGDNFVSGERQLLCIARALLRHKILILDEATAAMDTDOLLITQETIREAFADCT
 MLTIAHRLHTVLGSDRIMVLAQGVVEFDTPSVLLSNDSSRFYAMFAAENKVAVKG

>ABCC6= MRP6= Multidrug Resistance Associated Protein 6
 MAAPAEPCAGQGVWVQTEPEPAATSLLSLCFLRTAGVWVPPMYLWVLGPIYLLFIHHHGRGYLWMSPLF
 KAKMVLGFALIVCTSSVAVALWKIQQGTPEAPEFLIHPTVWLTTMSFAVFLIHTERKKGVQSSGVLF
 YWLLCFVL PATNAQAAGAGFQSDPVRHLSTYLCLSLVVAQFVLSCLADQPPFFPEDPQQSNPCPETG
 AAPPSKATFWWSGLVWRGYRRLRPKDLWSLGRNSSEELVSRLKEKEMNRNSAARRHNKAIAFKRKG
 GSGMKAPETEPFLRQEGSQWRPLLKAIWQVHSTPLLGTLSLIISDVFRFTVPKLLSLFLEFIGDPKPP
 AWKGYLLAVLMFSLACLQTLFEQNMVRLKVLQMLRLSAITGLVYRKVALSSGSRKASAVGDVNLVS
 VDVQRLTESVLYLNLGLWLPVWVIVVCFVYLWQLLGPSTALIAVFLSLLPLNFFISKKRNNHQQEQMRQ
 KDSRRLTSSILRNSKTIKFWGEGAFDLRVLGIRGQELGALRTSGLLFSVLSVSFQVSTFLVALVFA
 VHTLVAENAMNAEKAFVTLTVLNLNKAQAFLPFSIHSVLQARVSFDRVLTFLCLEEVDPGVVDSSSSG
 SAAGKDCITTHSATFAWSQESPPCLHRIINLTVPQGLLAVVGPVAGKSSLLSALLGELSKVEGFVSI
 GAVAVVPQEAWVQNTSVVENVCFGQELDPWLERVLEACALQPDVDSFPEGIHTSIGQGMNLSGGQKQ
 RL SLARAVYRKAAYLLDDPLAALDAHVGQHVFNQVIGPGGLLQGTTRILVTHALHILPQADWITVLAN
 GAIAEMGSYQELQKRGALVCLLDQARQPGDRGEGETEPTGSTDPRGTSAGRPELRRERSIKSVPEK
 DRTTSEAQTVEPLDDPRAGWPAGKDSIQYGRVKATVHLAYLRAVGTPLCLYALFLFLCQQVASFCRGY
 WLSLWADDPVAGGQQTQAALRGGIFGLGLCLQAIGLFASMAAVLLGGARASRLLFQRLWVVRSPISF
 FERTPIGHLNLRFSKETDVTVDVDPDKLRSLLMYAFGLLEVLVAVATPLATVAILPLFLLYAGFQSL
 YVSSCQLRRLLESASYSSVCSHMAETFGQSTVVRAFRTQAPFVAQNNARVDESQRI SP PRLVADRWLAA
 NVELLGNGLVFAATCAVL SKAHL SAGLVGFSVSAALQVTQTLQWVVRNWTLENSIVSVERMQDYAWT
 PKEAIPWRLPCCAQFPWQGGQIEFRDFGLRYRPELPLAVQGVSFKIHAGEKVGIVGRTGAGKSSLASG
 LLRLQEAEEGGIWDGVPPIAHVGLHTLRSRISIIIPQDPILFPGLSRMNLDDLQEHSDAIAWAALETVQL
 KALVASLPGQLQYKCADRGEDLSVGQKQLLCLARALLRKTQILILDEATAAVDPGTQLQMAMLSWFA
 QCTVLLIAHRLRSVMDCARVLVMDKGQVAESGSPAQLLAQKGLFYRLAQESGLV

>ABCC7= cystic fibrosis transmembrane conductance regulator
 MQRSPLEKASVSVSKLFFSWTRPILRKGYRQRLLESDIYQIPSVDSADNLSKLEREWDRRELASKKNPKL
 INALRRCFWRFMYGIFLYLGEVTKAVQPLLGRITASYDPDNKEERSIAIYLGIGLCLLFIVRTL
 HPAIFGLHHIGMQRIAMFSLIYKTKLSSRLDKISIGQLVSLSNLNKFDGLALAHFVWIAPLQ
 VALLMGLIWELLQASAFCGLGLFLVLAFLQAGLGRMMKRYDRQAGKISERLVITSEMENIQSVKAYC
 WEEAMEKMIENLRQTELKTRKAAVRYFNSSAFFFGFVFLSVLPYALIKGIIILRKIFTTISFCIV
 LRMAVTRQFPWAVQWYDSLGAINKIQDPLQKQEKLEYNLTTTEVVMENVTAFWEEGFGELFEKAKQ
 NNNNRKTSNGDSSLFFSNFSLGTPVLKDINFKIERGQLLAVAGSTGAGKTSLLMMIMGELEPSEGKIK
 HSGRISFCSQFSWIMPPTIKENIIFGVSVDEYRYSVIKACQLEEDISKFAEKDNIVLGEGGITLGGQ
 RARISLARAVYKADLYLLDSPFGYLDVLTKEIFEESCCKLMANKTRILVTSKMEHLKKADKILILHE
 GSSYFYGTFSLEQLNLQPDFSSKLMGCDSDQFSAERRNSILTETLHRFSLBGDAPVSWTETKKQSFQKT
 GEFGEKRNKNSILNPIINSIRKFSIVQKTPQNGI ZEDSDEPLERRLSLVPDSEQGEAILPRISVISTGP
 TLQARRRQSVNLNMTHSVNGQNIHRKTTASTRKVSLAPQANLTEDIYSRRLSQETGLEISEEINeed
 LKECFDDMESIPAVTTWNTYLYRITVHKSILIFVLWCLVIFLAEVAASLVVLWLLGNTPLQDKGNSTH
 SRNNSYAVIITSTSSYYVFYIYVGVDTLAMGFFRGLPLVHTLITVSKILHHKMLHSLVQAPMSTLNT
 LKAGGILNRFKSDIAILLDDLLPLTIFDFIQLLLLVIGAI AVAVLQPYIFVATVPVIVAFIMLRAYFLQ
 TSQQLKQLESEGRSPIFTHLVTSLKGLWTLRAFGRQPYFETLFHKALNLHTANWFLYLSTLRWFQMRIE
 MIFVIFFIATVFI SLTTGEGEGRGVGIETLAMNIMSTLQWAVNSSIDVDSLMSVSRVFKFIDMPTEG
 KPTKSTKPYKNGQLSKVMI IENSHVKDDIWPSGGQMTVKDLTAKYTEGGNAILENISFSISPGQVRGL
 LGRTGSGKSTLLSAFLRLNTEGEIQIDGVSWDSITLQWRAKFGVLPQKVFIFSGTFRKNLDPYEQWS
 DQEIWKVADEVGLRSVIEQFPGLKDFVLVDGCVLSHGKQLMCLARSVLSKAKILLDEPSAHLDPVT
 YQIIRRTLKQAFADCTVILCEHRIEAMLECCQFLVIEENKVRQYDSIQKLLNRSLSFRQATSPSDRVKL
 PPHNNSKCKSKPQIAALKEETEVEEQDTRL

>ABCC8=SUR1=Sulfonurea Receptor 1

Figure 3 - 9

MPLAFCGSENHSAAYRVDQGVLMNGCFVDALNVVPHVFLFITFPILFIGWGSQSSKVHIIHSTWHLHFP
 GHNLRWILTFMFLFVLVCEIAEGILSDGVTESHHLHLYMPAGMAFMAAVTSVVYHNIETSNFPKLLIA
 LLVYWTAFITKTIKFVKLLDHAIGFSQLRFCLTGLLVILYGMILLVEVNVIRVRRYIFFKTPREVKPP
 EDLQDLGVRFLQPFVNLPSKGTYYWMMNAFIKTAHKKPIDLRAIGKLPVIMRALTNYQRLCEAFDAQVRK
 DIQGTQGARAIWQALSHAFGRRLVLSSTFRILADLLGFAGPLCIFGIVDHLGKENDVFPKTPQFLGVYF
 VSSQEFANAYVLAVLLFLALLQRTFLQASYVVAIETGINLRGAIQTKIYNKIMHLSTSNLSMGEMTA
 GQICNLVAIDTNQMLMWFPLCPNLWAMPVQIIVGVILLYYILGVSALIGAAVILLAPVQYFVATKLSQ
 AQRSTLEYSNERLKQTNEMLRGIKLLKLYAWENIFTRVETTRRKEMTSLRAFAIYTSISIFMNTAIP
 AAVLITFVGHVSFKEADFSFSAFASLSLPHILVTPLFLLSSVVRSTVKALVSVQKLSEFLSSAEIRE
 EQCAPHEPTPQGPASKYQAVPLRVVNRKRPAREDCRGLTGPLQSLVPSADGDADNCCVQIMGGYFTWTP
 DGIPTLSNITIRIPRGQLTMIIVGQVCGCKSSLLAALGEMQKVSGAVFWSSLPDSEIGEDPSPERETAT
 DLDIRKRPVAYASQKPNWLLNATVEENIFESPFNKQRYKMIZACSLQPDIDILPHGDQTOIGERGIN
 LSGQQRRLSVARALYQHANNVFLDDPFSAIDHLSHLMQAGILELLRDDKRTVVLVTHKLQYLPHAD
 WIIAMKDGITQREGTLKDFORSECQLFEHWKTLMNQDQLEKETVTERKATEPPQGLSRAMSRSRDLGL
 QDEEEEEEEAAEEDDNLSSMLHQRAEIPWRACAKYLSAGIILLSLVFSQLLKHMLVLAIDYWLAK
 WTDALTLTPAARNCSLQECTLDQTVYAMVFTVLCSLGIVLCVTSVTVEWTGLKVAKRLHRSLLNRI
 ILAPMRFFETTPGLSILNRFSSDCNTIDQHIPSTLECLSRSTLCSALAVISYVTPVFLVALLPLAVV
 CYFTQKYFRVASRDLQQLDDTTQLPLLSHFAETVEGLTTIRAFRYEARFQOKLEYTDSNNIASLFLTA
 ANRWLEVRMEYIGACVVLIAAVTSISNSLHRELSAGLVGLGLTYALMVSNNYLNWVRNLADMEIQLGAV
 KRIHGLLKTAEASYEGLLAPSLIPKNWPDQCKIQIQNLVRYDSSLKPVLLKHVNALISPGQKIGICGR
 GSGKSSPFLAFFRMVDTFEGHIIIDGDIRKLPHTLPSRLSIILOQDPVLFSGTIRFNLDPERKSDST
 LWEALEIAQLKLVKALPGGLDAITTEGGENFSQGRQLFCLARAFVRKTSIFIMDEATASIDMATENI
 LQKVMTAFADRTVVTIAHRVHTILSADLVIVLKRGAILEFDKPEKLLSRKDSVFASFVRADK

>ABCC9= SUR2= Sulfonurea Receptor 2

MSLSFCGNNISSYNINDGVLQNSCFVDALNVVPHVFLFITFPILFIGWGSQSSKVQIHHNTWHLHFP
 NLRWILTFALLFVHVCEIAEGIVSDSRRESRHLHLMFPAVMGFVATTTISIVYHNIETSNFPKLLALF
 LYWMAFITKTIKLVKYCQSGLDISNLRFCITGMMVILNGLLMAVEINVIRVRRYVFFMNPQKVPPED
 LQDLGVRFLQPFVNLPSKGTYYWMMNAFIKTAHKKPIDLKAIGKLPAMRAVNTNYVCLDAYEEQKKKVA
 DHPNRTPSIWLAMYRAFGRPILLSSTFRYLADLLGFAGPLCISGIVQVNETQNGTNTTGTISETLSSK
 EFLNAYVLAVLLFLALLQRTFLQASYVVAIETGINLRGALLAMYNKILRLSTSNLSMGEMTLGQIN
 NLVAIETNQLMWFPLCPNLWAMPVQIIMGVILLYNLLGSSALVGAAVIVLLAPIQYFIATKLABAQS
 TLDYSTERLKTNEILKGIKLLKLYAWEHIKCSVEETRMKELSSKTPALYTSLSIFMNAIPIAAVL
 ATFWTHAYASGNLKPAAEFASLSLPHILVTPLSLFTVVRFAVKAIISVQKLEFLLSDEIGDSSWRT
 GESSLPFESCKKHTGVQPKTINRKQPGRYHLDSEYEQSTRRLRPAETEDIAIKVTNGYFVSWGSLATLSN
 IDIRIPTGQLTMIIVGQVCGCKSSLLAALGEMQTLLEGKVHNSNVNESEPSFEATRNRNRYSVAYAAQKP
 WLLNATVEENITFGSPFNKQRYKAVTDACSLQPDIDLLPFGDQTEIGERGINLSSGQRQRCVARALYQ
 NTNIVFLDDPFSAIDHLSHLMQEGILKFLQDDKRTLVLVTHKLQYLTHADWIIAMKDGSVLREGTLK
 DIQTKDVELYEHWKTLMNRQDQLEKMEADQTLERKTLRRAMYSREAKAQMEDEEEEEEEEDD
 MSTVMRLRTKMPKWCWRYLTSGGFFLLILMIFSKLLKHSVIVADYWLATWTSEYSINNTGKADQTTY
 VAGPSILCAGAFICLVTSITVEWMGLTAAKNLHNNLKNKIIILGPTRFDDTTPGLILNRFSAITNIID
 QHIPPTLESITRSTLLCLSAIGMISYATPVFLVALLPLGVAFYFIQKYFRVASKDLQELDDSTQLPLLC
 HFSETAEGLTTRAFRHETRFKQRMLELTDNNIAYLFLSAANRWLEVRTDYLGACIVLTASIASISGS
 SNSGLVGLGLLYALTITNYLNWVRNLADLEVQMGAVKVNSTFMESENVEGTMDFPSQVPEHWQEGE
 IKIHDLCVRYENNLKPVLLKHVKAIKPKQKVGICGRGSGKSSLSLAFRMVDIFDGKIVIDGIDISKL
 PLHTLRSRLSIILOQDPILFSGSIRFNLDPECKCTDDRLWEALEIAQLKNMVKSLPGGLDAVVTEGENF
 SVGQRQLFCLARAFVRKSSILIMDEATASIDMATENILQKVMTAFADRTVVTMAHRVSSIMDAGLVV
 FSEGILVECDTVPNLFAHKNPSTLVMTNK

>ABCC10 (partial sequence)

GSGCLGAEKREGKNRWQGEASMERLLAQLCGSSAAWPLPLWEGDTTGHCFTQLVLSPHALLAVLSAC
 YLGTTPRSPDYILPCSPGWRLRLAASFLLSVFPLLDLLPVALPPGAGPGPIGLEVLACVAAVAVISHSL
 ALWVLAHSPHGSRGPLALVALLPAPALVLTVLWHCQRTGLLPPLPGPMARLCLLILQLAALLAYA
 LGWAAPEGPREPWAQEPLLPEDQEPEVAEDGESWLSRFSYAWLAPLLARGACGELRQPDICRLPHRLQ
 PTYLARVFAHAWQEGARLWRALYGAFGRCYLALGELKLVTMLGFGSGLLLSLVGFLEEGQEPLSHGL
 LYALGLAGGAVLGAVLQNYGYEYVKVTLQARGAVNLILYCKALQLGSPRPPTGEALNLLGTDSERLN
 FAGSFHEAWGLPLQLAITLYLLYQVGVAFVGGILALLVPVNVKIATRIMASNOEMQLQHKDARVKLV
 TELLSGIRVIFKFCGWEQALGARVEACRARELGRLRVIKYLDAAVCYLWALPVVISIVIFTYVLMGHQ
 LTATKVTALALVRLMILPLNNFPWVINGLLEAKVSLDRIQLFLDLPNNHPQAYYSPDPPAEPSTVLEL
 HGALFVSWDPVGTSLETFISHLEVKKMGLVGVIGKVGCGKSSLLAAGELHRLRGHVAVRGLSKGFGLA
 TQEPWIOFATIRDNILFGKTFDAQLYKEVLEACALNDDLSILPAGDQTEVGKEGVTLSGGQRARIAR
 AVYQEKELYLLDDPLAAVDADVANHLLHRCILGMSYTTTRLLCTHRTYLERADAVLLMEAGRLIRAGP
 PSEILPLVQAVPKAWAENGQESDSTAQSVQNPKEKTEGLEEEQSTSGRLLQEESSKEGAVALHVYQAY
 WKAVGQGLALAILFSLLLMQATRNAADWLSHWISQLKAENSSQEAQSTSPASMGFLSPQLLLFSFGN
 LYIPVFLPLXAPNGSSDIRFYLTIVYATAGVNSLCTLLRAVLFAAGTLQAAATLHRRLLHRLVLMAPVT

Figure 3 - 10

FFNATPTGRILNRFSSDVACADDSLPFILNILLANAAGLLGLLAVLGSGLPWLLLLLPPLSIMYTHVQR
 HYRASSRRLRLGSLTSPLYSHLADTLAGLSVLRTATGTYRFEENRLLLELNQRCQFATSATMQWLD
 IRLQLMGAAVVSIAIGIALVQHQQGLANPGLVGLSLSYALSLTGLLSGLVSSFTQTEAMLVSVRLEEY
 TCDLPQEPQGPQLQGLTGWLTQGGVEFDQVVLAYRPLNALDGVTFVCVQPGKLGIVGRTGSGKSSLL
 LVLFRLLPESSGRVLLDGVDTSQLELAQLRSQLAIIQBPFLFSGTVRENLDPQGLHKDRALWQALKQC
 HLEVTITSMGGLDGELGEGGRSLSGQRQLCLARALLTDAKILCIDEATASVDQKTDQLLQQTICKRF
 ANKTVLTIAHRLNTILNSDRVLVLQAGRVVELDSPATLRNQPHSLFQQLQSSQGVASLGGP

>ABCD1=ALDP= adrenoleukodystrophy protein

MPVLSRPRPWRGNTLKRFAVLLAAYGAHKVYPLVRQCLAPARGLQAPAGEPTQEAAGVAAAKAGMNR
 VFLQRLWLLRLLFPRLVLCRETGLLALHSAALVSRTFLSVYVARLDGRLARCIVRKDPRAFGWQLLQWL
 LIALPATFVNSAIRYLEGQLALSFRSRLVAHAYRLYFSQTTYRVSNMDGRLRNPQSLTEDVVAFAAS
 VAHLYSNLTKPLLDVAVTSYTLRAARSRGAGTAWPSAIAGLVVFLETANVLRASFSPKFGELVAEEARRK
 GELRYMHSRVVANSEETAFYGGHEVELALLQSYQDLASQINLILLERLWYVMLEQFLMKYVWSASGLL
 MVAVPIITATGYSESDAEAVKKAALKKEEELVSETEAFTIARNLLTAAADAIERIMSSYKEVTELAG
 YTARVHEMFQVFEDVQRCFKRPRELEDAQAGSGTIGRSGVRVEGPLKIRGQVVDVEQGIICENIPIVT
 PSGEVVASLNIRVEEGMHLLITGPNCGCKSSLFRILGGLWPTYGGVLYKPPQPMFYIPQRPYMSVGS
 LRDQVIYIPDSVEDMQRGYSEQDLEAILDVVHLHILHILQREGGWEAMCDWKDVLSSGGEKQRIQMARMFYH
 RPKYALLDECTSAVSIIDVEGKIPOAAKDAGIALLSITHRPSLWKYHTHLQFDGEGGWKFEKLDAAARL
 SLTEEKQRLQEQLAGIPKMQRRLQELCQILGEAVAPAHVAPSPQGGGLQGAST

>ABCD2=ALDR= adrenoleukodystrophy related protein

MTHMLNAAADRVKWRSSAAKRAACLVAAAYALKTYPIIGKRLKQSGHGKKAAYPAAENTEILHCT
 ETICEKPSPGVNADFFKQLLELRKILFPKLVTTETGWLCLHSVALISRTFLSIYVAGLDGKIVKSIVEK
 KPRTFIILIKLWLMIAIPATFVNSAIRYLECKLALAFRTRLVDHAYETYFTNQTYKVINMDGRLANPD
 QSLTEDIMHMFQSVVAHLYSNLTKPILDMVLTSTYTLIQTATSRGASPIGPTLLAGLVVYATAKVLKACSP
 KFGKLVAAEAHRKGYLRVVSRIIANVEEIAFYRGHKVEMKQLQKSYKALADQMNILSKRLWYIMIEQ
 FLMKYVWSSSGLIMVAIPIITATGADGEDGQKQVMVSETEAFTARNLLASGADAIERIMSSYKEVT
 ELAGYETARVYNNMFVDFEVKRGYIKRTAVIQESSEHSKNGAKVELPLSDTLAIKGVIVDVHIGICENV
 PIITPAGEVVASRLNFKVEEGMHLLITGPNCGCKSSLFRILSGLWPVYEGVLYKPPQPMFYIPQRPYM
 SLGSLRDQVIYIPDSVDDMDKGYTDQDLERILHNHLYHIVQREGGWDVMDWKDVLSSGGEKQRMGMAR
 MFYHKPKYALLDECTSAVSIIDVEGKIPOAAKGAGISLLSITHRPSLWKYHTHLQFDGEGGWRFQELDT
 AIRLTLSEKQKLESQLAGIPKMQRRLNELCKILGEDSVLTKIKNEDETS

>ABCD3=PXMP1= Peroxisomal membrane protein 1

MAAFSKYLTARNSSLAGAFLLLCLLHKRRRALGLHGKSGKPLQNNKEGKKERAVVDKVFVSRLLIQ
 ILKIMVPRTFCKETGYLVLIAMVLSRTYCDVWMIQNGTLIESGIIGSRKDFKRYLLNFIAAMPLISL
 VNNFLKYGLNELKLCFRVRLTKYLYEELQAFYTYKMGNLDNRANPDQLLTQDVEKFCNSVVDLYSNL
 SKPFLDITVLYIFKLTSAIGAQQPASMMAYLVVSGFLTRLRRLPIGKMTITEQKYEGEYRVNSRLITNS
 EEIAFYNGNKRKQTVHVSFRKLVHNLHNFILFRFSGFIDSIIAKYLATVVGYLVVSRPFLDLHSHPRH
 LKSTHSELLEDYQSGRMLLRMSQALGRIVLAGREMTLAGFTARITELMQVLKDLNHHGKYERTMVSQQ
 EKGIEGQVITPLIPAGEIILADNI IKFDHVPLATPNGDVLIRDLNFEVRSGANVLICGPNCGCKSSLF
 RVLGELWPLFEGGRITKPERGKLFYVQRPYMTLGTLDQVIYPDGREDQKRKGISDLVLKEYLDNVQLG
 HILEREQGWDSVQWMDVLSGGEKQRMAMARLFYHKPQFAILDECTSAVSVDVEGYIYSHCRKVGITLP
 TVSHRKSLLWKHIEYLLHMDGRGNYEFKQITEDTVEFGS

>ABCD4=PXMP1L= Peroxisomal membrane protein 1-like 1

MAVAGPAPGAGARPRLDLQFLQRLQILKVLFPSSWSSQNALMFLTLCLTLLEQFVIYQVGLIPSQYYG
 VLGNDLEGPKTLTFLAVMLIVLNSLTKSFDQFTCNLLYVSWRKDLTEHLHRLYFRGRAYTTLNVLRDD
 IDNPQORISQDVERFCRQLSSMASKLII SPFTLVYTYQCFQSTGWLGPVSIFGYVILGTVVNTLMGP
 IVMKLVHQELEGDFRFXHMQIRVNAEPAAFYRAGHVEHMTDRRLQRLLOTQRELMSKELWLYIGINT
 FDYLGSIYSVYVIAIPFSGVYGDLSAELSTLVSKNAFVCYILISCTQLIDLSTLSDVAGYTHRIG
 QLRETLDMLSKSDCEILGESEWGLDTPPGWPAAPADTAFLLERVSIAPSSDKPLIKDLSLKISEG
 QSLITGNTGTGKTSLLRVLGGLWTSTRGSVQMLTDFGPHGVFLFPQKPPFTDGLTREQVIYPLKEVYP
 DSGSADDERILRFLAAGLSNLVARTEGLDQQVDWNYDVLSPGEMQRLSFARLFYLPKYAVLDEATS
 ALTEEVESELYRIGQQLGMTFISVGHRSQLEKPHSLVLKLCGGGRWELMRIKVE

>ABCE1= Ribonuclease L inhibitor

MADKLTRIAIVNHDCKPKKCRQCKKSCPVVRMGKLCIEVTPQSKIAWISETLCIGCGICIKKCPFGA
 LSIVNLPSNLEKETHTRYCANAFKLHRLPIPRPGEVLGLVGTNGIGKSAALKILAGKQKPNLGKYDDPP
 DWQEILTYFRGSELQNYFTKILEDDLKAIIPQYVARFLRLAKGTVGSILDRKDETKTQAIVCQQLDLT
 HLKERNVEDLSGGELQRFACAVVCIQKADIFMPDEPSSYLDVKQRLKAAITIRSLINPDRIYIIVVEHDL
 SVLDYLSDFICCLYGVPSAYGVVTMPFSVREGINIFLDGYVPTENLRFDASLVFKAETANEEVVKM
 CMYKYPGMKKMKGEFELAIIVAGEFTDSEIMVMLGNGTGKTTFIRMLAGRLKPDEGGEVPLNVSYKPKQ
 KISPKSTGSVRQLLHEKIRDAYTHPQFVTDVMPKPLQIENIIDQEVQTLSSGGELOVRVRLRLCLGKPADVY

Figure 3 - 11

LIDEP SAYLDSEQR LMAARVVKRFILHAKKTAFVVEHDFIMATY LADRVIVFDGVPSKNTVANSPTLL
AGMNKFLS QLEITFRDPNNYRPRINKLNSIKDVEQKSGNYFFLDD

>ABCF1

MPKAPKQPPPEWIGDGESTSPSDKVVKGGKKDKIKKTFEELAVEDKQAGEEEKVLKEKEQOQQQQQ
QOQQKKRDRTRKGRKKDDVDDGEEKELMERLKKLSVPTSDEEDVPAPKPRGGKKTGGNVFAALI QD
QSEEEEEEEKHPPKPAKPEKNRINKAVSEEQPALKGGKKEEKS KGAKPQNKPAALDNEEDKKEEI
IKEKEPPKQGEKAKKAEQMEYERQVASLKAANAENDFSVSQAEMSSRQAMLENASDIKLEKFSISAH
GKELFVNADLYIVAGRRYGLVGPNGKGTTLKXIANRALSIPPNI DVLLCEQEVVADETPAVQAVLRA
DTKRLKLEEBERRLQCGLEQDDTAERLEKVYEELRATGAAAAEAKARRILAGLGFDPQMQRPTQKF
SGGWRMRVSLARALFMEPTLLMLDEPTNHLDLNAVIWLNLYLQGWKRTLLIVSHDQGFLLDDVCTDIHL
DAQRLHYRGNMTFKMYQQKQKELLKQYEQEKKLKEKAGGKSTKQAEKQTKALTRKQKCRKN
QDEESQEAPELLKRPKEYTVRFTFPDPPPLSPVVLGLHGVTFGYQGOKPLFKNLDFGIDMDSRICIVGP
NGVGKSTLLLLTGKLTPTHGEMRNHRLKIGFPNQYAEQLRMEETPTEYLQRGFNLPYQDARKCLGR
FGLESHAHTI QICKLGGQKARVVAELACREPDVILDEPTNNLDIESIDALGEAINEYKGAIVVSH
DARLITETNCQLWVVEEQSVSQIDGDFEDYKREVL EALGEVMVSRPRE

>ABCF2

MPSDLAKKKA AKKKEAAKARQRPRKGHEENG DVVTEPQVAERNEANGRETTEVDLLTKELEDFEMKAA
ARAVTGVLAHPNSTDVHIINLSLTFHGQELLSDTKLELNSGRYGLIGLNGIGKSMLLSAIGKREVP
PEHIDIYHLTREMPPSDKTPHLCVMEVDTERAMLEKEAERLAHEDAECEKLMELYERLEELDADKAEMR
ASRILHGLGFTFAMQKKLKD FSGGWRMRVALARALFIRPFMLLLDEPTNHLDLDACVWLEELKTFKR
ILVLVSHSQDFLNGVCTNIIMHNKLLKYTGNVDQYVKTRELEENQMKRPFHWEQDQIAHMKNYIARF
GHGSAKLARQAQSKETLQKMMASGLTERVVS DKTLSFYFPFGKIPPPVIMVQNVSFKYTKDGPDIYN
NLEFGIDLDELVALVGPNGAGKSTLLKLTGELLPTDGMIRKSHSVKIGRYHQHLQEQLDLDLSPIEYM
MKCYPEIKEKEEMRKIIGRYLTKGQQVSPIRNLS DGQKCRVCLAWLAWQNPMLFLDEPTNHLDIETI
DALADAINEFEGGMLLVSHDFRLIQQVAQEIWVCEKQTITKWPGDILAYKEHLKSLVDEEPQLTKRTH
NVCTLTLASLPRP

>ABCF3

MATCAEILRSEFPPEIDGQVFDYVTGVLHSGSADFESVDDLVEAVGELLQEVSGDSKDDAGIRAVCQRM
NTLRLAEPQSQNSQVLLDAPIQLSKITENYDCGTKLPGLLKREQSSTVNAKKLEKAEARLKAKQEKRS
EKDTLTKSNPLVLEEASASQAGSRKESRLSSGKNKSYDVRIENFDVSGFDRVLLAGADVNLAWGRRY
LVGRNGLGKTTLLKMLATRLVRPAHISLHVEQEVAGDDTPALQSVLESDSVREDLLRRERELTAQIA
AGRAEGSEAEELAEIYAKLEIEADKAPARASVILAGLGFTPKMQQQPTREFSGGWRMLALARALFAR
PDLLELDEPTNMLDVRILWLENYLTWPSTILVSHDRNFLNAIATDIHLHSQRLDGYRGDFETFIK
SKQERLLNQREYEAQQYRQHIQVFIDFRYNANRASQVQSKMLKELPELRPVKESEVVMKFPDG
FEKFSPPILQLDEVDYDPKHVIFSRLSVADLESRICVVGENGAGKSTMLKLLGLDAPVRGIRHAH
RNLKIGYFSQHVEQLDLNVSAVELLARKFPGRPEEYRHQLGRYGISGELAMRPLASLSGGQKSRVAF
AQMTMPCPNFYILDEPTNHLDMETIEALGRALNNFRGGVILVSHDERPILVCRELWVCEGGGVTRVEG
GFDQYRALLQEQRREGFL

>ABCG1=ABC8 WHITE protein homolog

MAAFSVGTAMNASSYSAEMTEPKSVCSVDEVVSSNMEATETDLLNGHLKKVDNNLTEAQRFS SLPRA
AVNIEFRDLSYVPEGPWRRKKGYKTLKLGISGKFNSELVAIMGPSGAGKSTLMNLAGYRETGMKGA
VLINGLPRDLRCFRKVCYIMQDDMLPLHTVQEAMMVAHLKLQEKDEGRRENVKEILTALGLLSCAN
TRTGSLSGGQRKRLAIALELVNPPVMFFDEPTSGLDASCFQVVS LMKGLAQGGRSIICTIHQPSAKL
FELEDQLYVLSSQGCYVRGKVCNLPYLRLDLGLNCPYHNPADFVMEVASGEYGDQNSRLVRVREGMC
DSDHKRDLGGDAEVNPFVWHRPSEEVKQTKRLKGLRKDSSMEGCHSFASCLTQFCILFKRTFLSIMR
DSVLTHLRITSHIGLIGLLYLIGNETKKVLSNSGFLFFSMLFLMFAALMPTVLTFFPLEMGVFLRE
HLNYWYSLKAYYLAKTADVPFQIMFPVAYCSIVYWMTSQPSDAVRFLVFAALGTMTSLVAQSLGLLIG
AASTSLQVATFVGPTAIPVLLFSGFFVSDTPTIPTYLQWMSYISYVRYGFEVILSIYGLDREDLHCDI
DETFHQKSEA ILRELVDENAKLYLDFIVLGIFFI SLRLIAYVLRYKIRAER

>ABCC2= BCRP or Breast Cancer Resistance Protein

MSSSNVEVFIPVSGQNTNGFPATVSNDLKAFTEGAVLSFHNICYRVKLSGFLPCRKPVEKEILSNING
IMKPLGNAILGPTGGKSSLLDVLAARKDPSGLSGDV LINGAPRANFKCNSGYVVQDDVVMGTLTVRE
NLQFSAALRLATMTNHEKNERINRVIEELGLDKVADSKVGTQFIRGVSGGERKRTSIGMELITDPSIL
SLDEPTTGLDSSSTANAVLLLLKRMKSQGRTIIFS IHQPRYSIFKLFDSTLLASGRMLFHGPAQEALGY
FESAGYHCAYNNPADFLDIINGDSTAVALNREEDFKATEIEPSKQDKPLIEKLAEIYVNSFFYKET
KAELHQLSGGKKKKTIVFKEISYTTSTFCHQLRWVSKRSFKNLLGNPQASIAQIIIVTVVLGLVIGAIYF
GLKNDSTGIGNRAGVLFLLTTNQCFSSVSAVELFVVEKKLFIHEYISGYRVSSYFLGKLLSDLLPMRM
LPSIIFTCTIVYFMLGLKPKADAFVMMFTLMVAYSSASSMALAIAAGQSVSVATLLMTICFVMMIFFS
GLLVNLTIIASWLSWLQYFSIPRYGFTALQHNEFLGQNFPCPLNATGMNPNYATCTGEEYLVKQGIDL
SPWGLWKNHVALACMIVIFLT IAYLKLLFLKKYS

Figure 3 - 12

>ABCG5
MGDLSSLTPGSGMGLQVNRGSQSSLEGAPATAPEPHSLGILHASYSVSHRVRPWWDTSCRQQTROIL
KDVSLVYESGQIMCILGSSSGSKTTLDDAMSGRLGRAGTFLGEVYVNGRALRREQFQDCFSYVLQSDTL
LSSSLTVRETLYHTALLAIRRGNGPSFQKKVEAVMAELSLSHVADRLIGNYSLGGISTGERRRVSIAAQL
LQDPKVMFLFPTTGLDCMTANQIVVLLVELARRNRIVVLTTHQPRSELQFLFDKIAILSPGELIFCGTPA
EMLDFNDGCGYPCPEHSNPFDFYMDLTSVDTQSKEREIETSKRVQMIESAYKKSAICHKTLKNIERMKH
LKTLLPMVPFKTKDSPGVFSKLGVLRLRVTRNLVRNKLAVITRLLQNLIMGLFLLFFVLVRVSRNVLKGA
QDRVGLLYQFVGATPYTGMNAVNLFPVLRVSDQESQDGLYQKWQMLLAYALHVLFPFSVVATMIFSSV
CYWTLGLHPEVARFGYFSAALLAPHLIGEFLLVLLGIVQNPINVSVALLSIAGVLVSGGFLRNIQE
MPIPKIISYFTFQKYCSEILVNEFYGLNFTCGSSNVSVTTNPMCAFTQGIQFIEKTCPGATSRFTMN
FLILYSFIPALVILGIVVPKIRDHLISR

>ABCG8
MAGKAAEERGLPKGATPQDTSGLQDRLFSSSEDNSLYFTYSQGPNTLEVRDLNYQVDLASQVPWFQELA
QFKMPWTSQSCQNSCELGIQNLSPKVRSGQMLAIISSGCGRASLLDVTGRGHGCKIKSGQIWINQGP
SSPQLVRKCVAHVRQHNQLLPNLTVRETLAFAQMRLEPRTFSQAQRDKRVEDVIAELRLRQCADTRVGN
MYVRGLSGGERRRVSIGVQLLWNPGLILDEPTSGLDSFTAHLNVLKLSRLAKGNRLVLISLHQPRSDI
FRLFLVLLMTSGTPIYLGAQHMYQYFTAIGYPCPRYSNPADFYVDLTSIDRRSRQELATREKAQSL
AALFLEKVRDLDDFLWKAETKDLDETCVSSVTPLDTNCLPSPTKMPGAVQQFTTLIRRQISNDFRDL
PTLLIHGAEEACLSMTIGFLYFGHSGIQLSFMDTAALLFMIGALIPFNVLDDVISKYSERAMLYEEL
DGLYTTGPPYFAKILGELPEHCAYIIYGMPTYWLANLRPGLQPFLLHFLVWLVVFCRIMALAAAL
LPTFHMASFFSNALYNSFYLAGGFMINLSSLWTPAWISKVSFLRWCFEGLMKIQFSRRTYKMPLGNLT
IAVSGDKILSVMELDSPLYAIYLVIGLSGGFMVLYVSLRFIKQKPSQDW

Bacterial Transporters (examples)

>LmrA= lincomycin resistance protein
MERGPQMANRIEGKAVDKTSIKHFVKLIRAAKPRYLFFVIGIVAGIIGTLIQLQVPMVQPLINSFGHG
VNGGVALVIALYIGSAAVSAIAAIVLGI FGESVVKNLRTVRWDMKIHLPVKYFDEVKTGEMSSRLAND
TTQVKNLIANSIPQAFSTIILLVGSIIIFMLQMQWRLTLAMI IAVPIVMLIMPPIMTFGQKIGWTRQDSL
ANFQGIASESLSEIRLVKSNAEKQASKKAENDVNALYKIGVKEAVFDGLMSPVMMLSMMLMIFGLLAY
GIYLISTGVMSLGTLLGMMMYLMNLIGVPTVATFFTELAKASGSTGRLTELLDEEQEVLHQGDSLDLE
GKTLSAHVDFAYDDSEQLHDISFEAQPNISIIAFAGPSGGGKSTIFSLLERFYQPTAGEITIGGQPID
SVSLENWRSQIGFVSQDSAIMAGTIRENLTYGLEGNFTDEDLWQVLDLAFARSFVENMPDQLNTEVGER
GVKISGGQRQLAIAARAFLRNPKILMLDEATASLDSESESMVQALDSL MKGRTTLVIAHRLSTIVDAD
KIYFIEKGETGSGKHNLVATHPLIYAKYVSEQLTVGQ

>DrrA=daunorubicin resistance protein
MNTQPTRAIETSGLVKYNTRAVDGLDLNVPAGLVYGLGPNAGKSTTIRMLATLLRPDGGTARVFG
HDVTSEEDTVRRRISVTGQYASVDEGLTGTENLVMMGRLQGYSWARARERAAELIDGFLGDARDRLK
TYSGGMRRLDIAASIVVTPDLLFLDEPTTGLDPRSRNQVWDIVRALVDAGTTVLLTTQYLDLADQLAD
RIAVIDHGRVIAEGTTGELKSSLSGNLRLRLHDAQSRAEARLLSAELGVTIHRSDPTALSARIDDP
RQGMRAELSRTHLEVRSPSLGQSSSLDEVFLALTGHPPADDRSTEEAAEEKVA

>OleB=oleandomycin resistance protein *Streptomyces coelicor*
MQNAHRSDTGAAALTGTPEKLLPTQPETGSFQVVLDDVVAPGGRPLLDGVNQSVVALGERVGIIGENG
GKSTLLRLAGVDRPDGGQVLVRAPGGCGYLPQTPDLPEDTVQDAIDHALAELRSLERGLREAEQALA
GA3PEELEGLLGAAGDLEAFEARGYAADARVDAAMHGLGLAGITGDRRLGSLSGGEQARLNACLLA
ASPQLMLLDEPTNHLVDGALEWLEERLRAHRGSVLVSHDRVFLERVATALWEVDGERRTVNRHGGYA
GYLQAKAAARRRWEQAYQDWLEDLARQRELARSADHLATGPRRNTESNRQRHQRNVEKQISARVRNAK
ERVRLLENPVRPPQPMRFARVEGGGTVGRGALAEYKVTVGTRLDVPSFTVDPGERILITGHNGA
GKSTLLRVLAGDLAPDQGECEPERIGWLPOETEITDRQSSLLAAFAAGLPGIAEEHRAAGLGFGLFRP
SALGTAVGDLSTGQLRLRLARLLRDPADLRLLEPTNHLSPALVEDLEALAHYRGALVVVSHDRMFA
QRFTGRRMHMEGGRFVE

PROTOZOA (examples)

>Pfmdr2= multidrug resistance protein 2 - malaria parasite
(Plasmodium falciparum)
MDVSNYEYLRSGIKNELKRRTHKKIIYHLLDIIFFLLFFSCYNPNLELCYKYEKAIFYNFFKSSV
DLFLLNVIRIIYTVILFRLHKKLTELNTLGKVYVLSRHITGILVILNVIKMINYSYIKSENPLYNTNM
YLITLKVLFMVYSMISIIYFYI QPKLYNIKKKYI IARVELEKILINDIKSKKYNIIKSDENSGLLGTD
NNSTIMNNEYLNLDYKNLLDMNISYNKLNKINNDIINNTSDVQEKMDYNDIHNFKKKKSSNFAYLN
PFHKESKDNKIDVKESEFLNKRYGSNKRSSKIYDNNNNNNNNNNNSKIDYLENNITYTEFKKILLPYLW

Figure 3 - 13

PSKRIDMKGNSILRTYIVLIFLPIFVSVKVSFVSPVILGWASNEVLKKSLSSSSVYVGLYVTFVFFISK
 FLKEVCGVLFPSQVQSAFIELQESIFQTFHNLSEYEWYSSKNSGGIMRIVDRGTESANNLMSSVLMYIIP
 ATIEGLITCIIIFIPKYKNSLGSVLFGLTLYIYSTIKITKWRKKIRTKANEMDNVYHDIAHDSLTNYE
 NVKYFSNEKFBKFKCNALSNYHRYNLKILNSLILNTVQQFILNGTLFFTLCTVIMIVKEGSDPGTF
 ISVVVYTSNVFAPLSILGTLTYATIIKSFTDISDLIDILRDKIDISNDKLNKNFDLTSQEKKFGVSIEFN
 NVHFNYPQPLHTSLKDINIYIKPGTTCALVGHTGSGKTTISKLLYRFYDSKGEIKIGGRNINEYTRNS
 IRNIIGIVPQDTILFNEISIKYNILYKGLDATEEELIQAVKSAQLYDFIQSLPKKWDTLVGDKGVKLSGG
 ERQRISIAARCLLKDPKIVIFDEATSSLDSTRTEYLFQKAVEDLRKNRTIIIIAHKLCITITAEELIILLNK
 GKI IERGTHDLLKCNGEYTEMMNMQSKSNEPHTETNSSIDKDDVNKNKNKNDVILATCKNDITTSFR
 SNSEKSSQFSAASNHKQSKTSNDHNNNINVHKNEQEQLFTNDKTDMDNMMNNKKK

>DVLQF=MDR-PLAFF= Pfmr1= chloroquine resistance protein (Plasmodium falciparum)

MGKEQKEKKDGNLSIKEEVEKELNKKSTAEFRKIKNEKISFFLPFKCLPAQHRKLLFISFVCAVLSSG
 TLPFFISVFGVILKNNMNGDDINPIILSLVSIGLVQFVILSMISSYCMDVITSKILKTLKLEYLRSVYFQ
 DQGFHNNPQSGKLRSDLDYFLEQVSSGIGTKFITIFTYASSFLGLYVSLIKNARLTLCITCVPLIYV
 CGVICHNNKVKLNKKTSLYNNNTMSIEEALMGIRTVASYGKTIILNKNLSETFYSKYILKANFVEA
 LHIGLINGLILVSYAFGFWYGTRIIINSATNQYPPNDFNGASVISILLGVLISMFLTIILPNITEYMK
 ALEATNSLYEIIINRKPLVENDDGETLPNIKKIEFNVRPHYDTRKDVBIYKOLSFTLKEGKYAFVGE
 SGCGKSTILKLIERLYDPTEGDIIVNDSHNLKDINLKWRSKIGVVSQDPLLPNSIKNNIKYSLYSLK
 DLEAMENYEEENTNDTYENKNFSLISNSMTSNELLEMKKEYQTIKDSDDVDVSKKVLHDFVSSLPDKY
 DTLVGSNASKLSGGQKQRISIAIRAIMRNPKILILDEATSSLDNKSEYLVQKTINNLKGNENRTIIIAH
 RLSTIRYANTIFVLNRRSDNN
 INNQKISSNKSNNNGNDNGSDNKSSAYKDSDTGNDADNMNLSIHNENISNNRNCKNTAENEKEEKVP
 FFRMRFRKKKAPNLRITTYKEIFSYKDDVTIIFFSILVAGGLYPVALLYARYVSTLFDANLEYNSN
 KYSIYILLIALAMFISETLKNYNNKIGEKVEKTKRRFLFENILYQEMSFDDQDKNTPGVLSAHINRV
 HLLKTGLVNNIVIPSHFIMLFLVSMVMSFFYFCPIVAAVLTFIYFINMRVFAVRARLTKSKEIEKKENMS
 SGVFASFSSDDDEMFKDPSFLIQEAFYNNMHTVINYGLEDYFCNLEKADYKNGQKRRRIIVNAALWGFQ
 SAQLFINSFAYWFGSFLIKRGTLVDDPMKSLFTTIFTGSYAGKLSMLKGDSENAKLSFEKYYPLMIRK
 SNIDVRDDGIRINKNLKGVKIDKVNFRYISRPNVPIYKNLSPTCDSKTTATVGETSGSKSTFMNL
 LLRFYDLKNDHIIILKNDMTNFQDYQNNNNNSLVKKNVNEFSNQSGSAEDYTVFNNGEILLDDINICDY
 NLRDLRNLFSIVSQEPMFLNMSIYENIKFGREDATLEDVVRVSKPAAIDEFIESLPNKYDTNVGPGYGS
 LSGGQKQRTAARALLREPKILLDEATSSLDNSSEKLEIKTIVDKDKADKTIITIAHRIASIKRSDK
 IVVFNPNDRNGTFVQSHGTHDELLSAQDGIYKYVKLAK

>DVLNS= Methothrexate resistance protein Leishmania tarentolae

MVDNQHVTIAMADLGTVEIAQVRCQQAQRKFAEQDELWGGEPAITPTVEDQASWFQQLYYGWIGDY
 IYKAAAGNITEADLPPPTSTRTRYHIGRKLRSQAADIDASRRWQGYIGCEVVYKSEARAKGVLRWVGH
 LQQSDYPRSLVAGVEWRMPRHRRLAVLGSAAALHNGVVGHERLFWPHEDNYLCSCEPVEQLYVKSXYN
 LIPPRPPSPDLRLTLFKVHWYHWAQILPKLLSDVTALMLPVLLBYFVKYLNADNATWGWGLGLALTI
 PLTNVQSCSAHKYDHSIRTAALFETSSMALFEKCFVSRSLQRPDMSSVGRIMNMVNDVDNIGSL
 NWYVMYFWSAFLQLVLCLLLIRLVGWLVRPGMAVLFVTLPLQAVISKHVQDVSEMASVVDLRKRTN
 ELLSGVRIVKFMGWEPVFLARIQDARSRELRLRDVHVANVFFMFVNDATPTLVIAVVFILYHVSQKVL
 KPEVVFETIALLNTRVSPFPIIISSILQCFVSAKRVTAFIECPDTHSQVDIASIDVPAADAFKQ
 ASIHTYLPVKLPCKSRSLTAMQSTLWFRRRGVPETEWYEVDSPDASASSLAVHSTTVHMGSTQVITD
 SDGAAGEDEKGEVEGDREYYQLVSKELLRNVSITI PKGKLTVMIGSTGSGKSTLLGALMGEYSVESGE
 LWAERSIAYVPQAWIMNATLRGNILFFDEERAEDLQDVTRCCQLEADLAQFCGGLDTEIGEMGVNLSG
 GQKARVSLARAVYANRDVYLLDDPLSALDAHVGQRIVQDVTLGRRLGKTRVLATHQIHLPLADYIVVL
 QHGSIVFAGDFAAFSATALEETLRGELKGSKDVESCSDDVDTESATAETAPYVAKAKGLNAEQETSLAG
 GEDPLRSDVEAGRLMTTEEKATGKVPWSTYVAYLKSCGGLAEGCLLATFALTECVTAASSVWLSIWST
 GSLMWSADTYLYVYLFIVFLEIFGSPRLRFFLCYYLIRIGSRNMHRDLLESIGVARMSSFFDTPFVGRVLN
 RFTKDMSTILDNTLNDGYLYLLEYFFSMCSTVIIMVVVQPFVLVAIVPCVYSYYKLMQVYNASNRTRRI
 KSIAHSPVFTLLEESLQGGRTIATYGLHLVLQALGRLDVVYSALYMNQVNSNRWLGVRLLEFLSCVVT?
 MVAFIGVIGKMBGASSQNI GLISLSTMSMTLETNLWLVRQVAMVEANMNSVERVLHYTQVEHEHVP
 EMGELVAQLVRSSESGRANVTETVIESAGAASSALHPVQAGSLVLEGVQMRYREGPLVLRGVSQIA
 PREKVGIVGRTGSGKSTLLLTFRMRVVEVCVGVHVNREMSAYGLRELRRHF SMIPQDPVLFDTGTVRQN
 VDPFLEASSAEVWAALVGLRERVASEGIDSRVLEGGSNYSVGQRQLMCMARALLKRGSGFILMDE
 ATANIDPALDRQIQATVMSAFSAYTVITIAHRLHTVAQYDKIIVMDHGVAEMGSPRELVMNHQSMFHS
 MVESLSRGSKDFYELLMGRRIVQPAVLSD

FUNGAL TRANSPORTERS (examples)

>Bfr1= Brefeldin A resistance protein Schizosaccharomyces pombe

MNQNSDTTHGQALGSTLNHTTEVTRISNSSDHFEDESSSNVDESLSNPPSSNEKASHTNEEYRSKGNQS
 YVPSSSNPSPSESSNSDSSSDSSVDRLAGDPFELGENFNLKHYLRAYKDSLQRDDIITRSSGVCMR
 DHSVYGVGSGYEFLKTFPDI FLQPYRAITEKQVVEKAILSHCHALANAGELVMVLGQPGSGCSTFLRSV

Figure 3 - 14

TSDTVHYKRVEGTHHYDGDIDKADMKKFFPGDLLYSGENDVHPSLTTAETLDFAAKCRTPNRPNCLTR
 QEYVSREHLIATAFGLTHTFNTKVGNDVFRGVSGGERKRVITISEGFATRPITACWDNSTRGLDSSSTAF
 EFVNVLRTCANELKMTSFVTAYQASEKIYKLFDRICVLVYAGRQIYYGPADKAKQYFLDMGFDCHPRETT
 PDPLTAISDPKARFPRKGFENRVPRTPEDEFQMWNRSSVYADLMAEMESYDKRWTTETTPASSEAPEKDN
 FGSDISATTKHLYRQSAVAEKSKRVKDTSPYTVTFSSQLWYCLARSWERYINDPAYIGSMAFAFLFQS
 LIIGSIFYDMKLTNDVDFSRGGVLFSSILFCALQSLSEIANMFSQRPIIAKHASALYHPAADVSSLI
 VDLPFRFINISVFSIVLYFLTNLKRRTAGGFWTYFLFLFIGATCMSAFRSLAGIMPVNESASALGGIGV
 LAIAIYTGAI PNIDVGWFRWIAYLDPQFGFESLMINEFKARQFECSQLIPYGSYDNYPVANKICP
 VTSAPPGTDYVDGSTYLYISFNKTRQLWRNLAIIGYYAFLVFNIVASETLNFDNLKGEYLVFRRGH
 APDAVKAANVEGCKPLDLETQDQTQGGDVVKESPDNEBELNKEYEGIEKHGDFSWRNLNYDIQIKGEH
 RRLNGVQGFVVPKLTALMGESGAGKTTLLNLVLAQRVDITGVVTDGMLVNGRGLDSTFQRRRTGYVQQQD
 VHIGESTVREALRFSALRQPASVPLSEKYEYVESVIKLEMSYAEAIIGTPGSGLNVEQKRATIGV
 ELAAKPAALLFLDEPTSGLDSSQSAWSIVCFLRKLADAGQAILCTIHQPSAVLFDQPDRLLLQKGGKTV
 YFGDIGESKTLNLYFESHGAVHCPDDGNPAEYILDVIGAGATATTNRDWHVWNNSEERKAISAELOK
 INASFSNSEDKKTLSKEDRSTYAMPLWFQVKMVMTRNFQSYWREPSILMSKLALDIFAGLFIGFTFYNQ
 GLGVQNIQNLKFAVFMATVLA VPLINGLQPKFIELRNVFEVREKPSNIYSWAFVFSATITVEIPNLV
 GTLFPCLWFYPIKFYKHIIHHPGDKTYAWLLYMFFQMYFSTFGQAVASACPNAQTASVUNSLFTFTVT
 FNGVLQPNNSNLVGFWHMHSLTPTTYLIEGLLSDLVHGLPVECKSHEMLTINPPSGQTCGEYMSAFLTN
 NTAAGNLLNPNAATTSCSYCPYQTADQPLERFSMRYTHRWNLGIFVGYVFFNTFAVLLLFYFVRVMKLR
 STWLGGKKTGTG

>Cdr1= multidrug resistance protein 1 *Candida albicans*
 MSDSKMSSQDESLEKAISSQSSSENHSINEYHGFDHTSENIONLARTFTTHDSFKDDSSAGLLKYLTH
 MSEVPGVNPYEEHEEINNDQLNPDSENFNAKFWVKNLRLKFESDPEYKPSKLGIGYRNLRAYGVANDSD
 YQPTVTNALWKLATETGFRHFQKDDDSRYFDILKSMDAIMRPGELTVVLGRPGAGCSTLLKTIADVNTYGF
 HIGKESQITYDGLSPHDIERYHGRDVIYSAETDVHFPHLVSGDTLEFAARLRTPQNRGEGIDRETYAKH
 MASVYMATYGLSHTRNTNVGNDVFRGVSGGERKRVSIABASLSGANIQCDWNATRGLD SATALEFIRAL
 KTSAVILDTTPLIAIYQCSQDAYDLFDKVVVLYEGYQIFFGKATKAKKEYFEKMGWKCPRQTTADFLTS
 LTNPAREPLPGYEDKVPRTAQEFETFWKNSPEYAEITKEIDEYFVECESNTRETYRESHVAKQSNNT
 RPASPYTVSFFMQVRYGVARNFLRMKGDPSPILISILSOLVMGLILASVFFNLRSQTGTSFYRGAMFF
 AVLNFASFSSLEIMSLFEARPIVEKHKYALYRPSADALASIISELVVKLAMSMSFNFFVFMVNRFRN
 PGRFFFYWLMCIWCTFVMSHLFRSIGAVSTISGAMTPATVLLAMVIYTGFIPTPSMLGWSRWINYI
 NPVGTVFESLMVNEFHGREFQCAQYVPSGPGYENISRSNQVCTAVGSPGNEMVSGTNYLAGAYQYNS
 HKWRNLGITIGFAVFFLAITYIALTEFNKGAMQKEIVLFLKGSLLKHKRKTAAASNKGDI EAGPVAGKLD
 YQDEAEAVNNEKFTKSGTGSVDFFPENREIFFWRDLYQVKIKKEDRVILDHVDGWKPGQITALMGAS
 GAGKTTLLNCLSERVTGTIITDGERLVNGHALDSSQFQSGYVQVQDDVHLPTSTVREALQFSAYLRQSN
 KISKEKDDYVDYVIDLEMTDYADALVGAGEGLNVEQKRRLTIGVELVAKPKLLFLDEPTSGLDQTA
 TAWSTCKLMLKADHGQAILCTIHQPSALIMAEFDRLLFLQKGGRTAYFGELGENCQTMINYFEKYGAD
 PCPKEANPAEWMLQVVGAA PGSHAKQDYFEVWRNSSEYQAVREEINRMEAE LSKLPRDNDPEALLKYAA
 PLWQYLLVSWRTIVQDWRSPGYIYSKILVLSAALFNGFSFPAKNNMQGLQNMFSVFMFFIPFNTL
 VQQLPYPVKQRDVEYVREAPSRFTSWFAFIAGQITSEIPYQVAVGTIAFFCWYYPGLYNNATPTDSV
 NPGVLMWMLVTAFAVYVYATMGQLCMSFSELADNAANLATTLLFTCLNFCVGLAGPDVLPGFWMFYRC
 NPFTYLVQAMLSLGLANTFVKCAEREYVSVKPPNGESCSTYLDPIYKFGGYFETRNDGSCAFQMSST
 NTFKLSVNSLYSERWRNFGIFIAFIAINIILTVIFYWLARVPKGNREKKNKK

>Cdr2= multidrug resistance protein 2 *Candida albicans*
 MSTANTLSQQLDENPWWASDNSSVQEQGFDATA SHNIQDLARKLTHGSTNGDHHSANDLARYLSHM
 SDIPGVSPFNGNI SHEQLDPDSENFNAKYVKNLKKLFESDSDYKPSKLGVA YRNLRAYGIANDSDYQ
 PTVTNALWKFTTEAINKLKKPDDSKYFDILKSMDAIMRPGELTVVLGRPGAGCSTLLKTIADVNTYGFHI
 GKESQITYDGLSPHDIERYHGRDVIYSAETDVHFPHLVSGDTLEFAARLRTPQNRGEGIDRETYAKHMA
 SVYMATYGLSHTRNTNVGNDVFRGVSGGERKRVSIABASLSGANIQCDWNATRGLD SATALEFIRALKT
 SATILDTTPLIAIYQCSQDAYELFDNVVLYEGYQIFFGKASKAKKEYFENMGWKCPRQTTADFLTSLT
 NPAEREPLPGYEDKVPRTAQEFETFWKNSPEYAEITKEIDEYFVECESNTGETYRESHVKGQSNNTRP
 SSPYTVSFFMQVRYVIARNFLRMKGDPSPILISILSOLVMGLILASVFFNLRSKSTDTFFYRGGALFFSV
 LFNAPSSLEILSLYEARPIVEKHKYALYRPSADALASIISELVVKLLMTMSFNIVYFVMVNLRRTAG
 NFFFYWLMCASCTLVMSHMFERSIGAVTTIATAMSLSTVFLAMIIYAGFVLPPIPYILGWSRWIRYINP
 VTYIFESLMVNEFHGREFCGQYIPSGPGFENLPVENKVCTTVGSTPGSTVVQGT EYIKLAYQFYSSHK
 WRNFGITVAFVFFLG VYVALTEFNKGASQKEIVLFLKGSLLKHKRKTAAASNKGDI EAGPVAGKLDYQ
 DEAEAVNNEKFTKSGTGSVDFFPENREIFFWRDLYQVKIKKEDRVILDHVDGWKPGQITALMGASGA
 GKTLLNCLSERVTGTIITDGERLVNGHALDSSQFQSGYVQVQDDVHLETTVREALQFSAYLRQSNKI
 SKKEKDDYVDYVIDLEMTDYADALVGAGEGLNVEQKRRLTIGVELVAKPKLLFLDEPTSGLDQTA
 WSICKLMRKLADHGQAILCTIHQPSALIMAEFDKLLFLQKGGRTAYFGELGENCQTMINYFEKYGADPC
 PKEANPAEWMLQVVGAA PGSHAKQDYFEVWRNSSEYQAVREEINRMEAE LSKLPRDNDPEALLKYAAPL
 WKQYLLVSWRTIVQDWRSPGYIYSKILVLSAALFNGFSFPAKNNMQGLQNMFAVFMFFVPTFTTID
 QMLPYFVKRAVYVREAPSRFTSWFAFIAGQITSEIPYQVAVGTISYFCWYYPGLYANAEPDTSVNS
 RGVLMWMLLTAFYVYVYATMGQLAISLNLIDNAANLATTLLFTCLMFCVGLAGPNVIPGFWMFYRCNP

Figure 3 - 15

FTYLIQAILSTGLANAKVTCAPRELVTLPKPPMGETCSSFIGPYTEAAGGYFSTNSDGTCSVCRIDSTNQ
FLESINALFSQRWRNFGIFVAFIGINIILTIFFYWLARVPKGNREKMKK

>Pdr5p= multidrug resistance transporter *Saccharomyces cerevisiae*
MPEAKLNNVNDVTSYSSASSSTENAADLHNYNGFDEHTEARIQKLARTLTAQSMQNSTQSAPNKSDAQ
SIFSSGVEGVNPIFSDPEAPGYDPKLDPNSENFSSAAWVKMAHLSAADPDFYKPYSLGCAWKNLSASG
ASADVAYQSTVVNIPYKILKSLRKFQRSKETNTFQILKPMGCLNPGELLVVLGRPGSGCTTLLKSIS
SNTHGFDLGADTKISYSGYSGDDIKKHFRGEVVYNAEADVHLPHLTVFETLVTVARLKTQPNRIKGVDR
ESYANHLAEVAMATYGLSHTRNTKVGNDIVRGVSGGERKRVSLAEVSIKSGKFCWDNATRGDLSATAL
EFIRALKTQADISNTSATVAIQCSQDAYDLFNKVCVLDGQYIYYGPADKAKKYPEDMGYVCPSRQTT
ADFLTSTVTSPTSERTLNKDMKKGIIHIPQTPKEMNDYVWVKSPPYKELMKEVDQRLNDDDEASREAIKEAH
IAKQSKRARPPSPYTVSYMMQVYKYLIRNMWRLRNIGFTLFMILGNCSMALILGSMFFKIMKKGDTST
FYFRGSAMFFAILFNAFSSLEIFSLYEAPITEKHRTYSLYHPSADAFASVLSEIPSKLIIAVCFNII
FYFLVDFFRRNGGVFFFYLLINIVAVFSMSHLFRCVGS�TKTLSEAMVPASMLLLALSMTYGFAPKPKKI
LRWSKWIWYINPLAYLFESELLINEFHGKIFPCAIEYVPRGPAYANISSTESVCTVVGAVPGQDYVLGDDF
IRGTYQYYHKDKWRGFGIGMAYVVFVFFVYLFLCEYNAGAKQKGEILVFRSIVKRMKRGVLTEKNAN
DPENVGSDLSDDRMLQESSEESDTEIGLSKSEAFHWRNLCYEVQIKAEFTRILNNVDGWVKP
GTLTALMGASGAGKTTLLDCLAERVMTGVITGDILVNGIPRDKSFPRSIGYQQQDLHLKTATVRESLR
FSAYLRQPAEVSIEKNRYVEEVIKILEMEKYADAVVGAGEGLNVEQRKRLTIGVELTAKPKLLVFLD
EPTSGLDSTAWISICQLMKLANHGQAILCTIHQPSAILMQEFDRLLFMRGQGGKTVYFGDLGEGCKTMI
DYFESHGAHKCPADANPAEWMLLEVGAAPGSHANQDYEVWRNSEEYRAVQSELDWMERELPKKGSITA
AEDKHEFSQSIYYQTKLVSIRLFQYWRSPDYLWSKFILTI FNQLF IGFTFFKAGTSLQGLQNQMLAVF
MFTVIFNPILOQYLPSPFVQQRDLYEARERPSRTFSWISFIFAQIFVEVPWNILAGTIAFYIYYPIGFI
SNASAGQLHERGALFWLFSCAFYVYVGSMLLVI SFNQVAESAANLASLFTMSLSFCGVMTPPSAMP
RFWIFMYRVSPLTYFIQALLAVGVANVDVKADYELLEFTPPSGMTCGQYMEPYLQAKTGYLTDENAT
DTCFSCQISTTNDYLANVNSFYSERWRNYGIFICYIAFNIIAGVFFYWLARVPKKNGLSKK

>Snq2P *Saccharomyces cerevisiae*
MSNIKSTQDSSHNAVARSASSAFAASEESFTGITHDKDEQSDTPADKLT KMLTGPARDTASQISATVSE
MAPDVVSKVESFADALSRHTTRSGAFNMDSDSDGDAHAIFESFVRDADEQGIHIRKAGVTIEDVSAK
GVDASALEGATFGNIIPLTIFKGIKAKRHQKMRQIISNVNALAEAGEMILVLRPGAGCSSFLKVTA
GEIDQFAGGVSGEAYDGIPOEEMMKRYKADVIYNGELDVHFPYLTVKQTLDFAIACKTPALRVNNVSK
KEYIASRRDLATIFGLRHTYNTKVGNDFVRGVSGGERKRVSLAEALAAKGSYICWDNATRGDASTAL
EYAKAIRIMTNLLKSTAFVTIYQASENIYETFDKVTLYSGKQIYFGLIHEAKPYFAKMGYLCPPRQAT
AEFLTALTDPNFGFLIKPGYENKVPRTAEFEFTYWLNSPEFAQMKKDIAAYKEKVNTKTEKVEYDESMA
QEKSKYTRKKSYYTVSYWEQVKLCTQRFQRIYGNKSYTVINVCSAIIQSFITGSLFYNTPSSTSGAFS
GGVLYFALLYYSMLGLANISFEHRPILQKHKGYSLYHPSAEATGSTLASFPFRMIGLTCFFIILFFLS
GLHRTAGSFFTIYFLTMCSEAINGLFEMVSSVCDTSLQANSISGILMMSISMYSTYMIQLPSMHPWFK
WISYVLPPIRYAFESMLNAEFHGRHMDCANTLVPSGGDYDNLSDDYKVCFAVGSKPGQSYVLGDDYLNQ
FOYVYKHTWRNFILWCFLLYVVLKVIFTEYKRPVKGGDALIFKKGSKRFLAHADEESPDNVNDIDA
KEQFSSESSEGANDEVFDDLEAKGVFIWKDVCTIPYEGGKRMLLDNVSGYCIPGTMTALMGESGAGKTT
LLNTLAQRNVGIIITGDMLVNRPIDASFERRTGYYQQDIHIAELTVRESLQFSARMRRPQHLDPSEKM
DYVEKIIIRVLGMEFYAEALVGEVGCGLNVEQRKLSIGVELVAKPDLLLFLDEPTSGLDSSSWAIIQL
LRKLSKAGQSILCTIHQPSATLFEEDRLLLRLKGGQTVYFGDIGKNSATILNYFERNGARKCDSSSEN
AEYILEAIGAGATASVKEDWHEKWLNSVEFEQTKKQVQDLINDLSKQETKSEVGDKPSKYATSYAYQFR
YVLIRTSTSFWRSLNYIMSKMMLLVGGLYIGFTFFNVGKSYVGLQNAMFAAFISIIISAPAMNQIQGR
AIASRELFEVRESQSNMFHWSLVLTQYLSLPYHLFFSTIFFVSSYFPLRIFFEASRSVAVFLNYCIM
FQLYYVGLGLMILYMSPNLPSANVILGLCLSFMLSFCGVTQPVSLMPGFWTFMWKASPTYTFVQNLVGI
MLHKKPVVCKKKELNYFNPPNGSTCGEYMKPFLEKATGYIENPDATSDCAYCIYEVGDNYLTHISSKYS
YLWRNFGIFWIYIFFNIIAMVCVYVLFHVRQSSFLSPVSIILNKIKNIRKKKQ



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

EP 00 87 0316

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
A	<p>DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; BIANCHET M A ET AL: "Modeling of nucleotide binding domains of ABC transporter proteins based on a F1-ATPase/recA topology: structural model of the nucleotide binding domains of the cystic fibrosis transmembrane conductance regulator (CFTR)" retrieved from STN Database accession no. 1998170885 XP002178151 & JOURNAL OF BIOENERGETICS AND BIOMEMBRANES, (1997 OCT) 29 (5) 503-24. , * abstract *</p> <p style="text-align: center;">— -/-</p>	1-39	<p>C12N15/11 C07K14/705 A61K38/17 G01N33/68</p>
			<p>TECHNICAL FIELDS SEARCHED (Int.Cl.7)</p> <p>C12N C07K A61K G01N</p>
<p>INCOMPLETE SEARCH</p> <p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search: see sheet C</p>			
Place of search		Date of completion of the search	Examiner
THE HAGUE		25 September 2001	Masturzo, P
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03.82 (P04007)



European Patent
Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 00 87 0316

Although claims 1-9 (at least partially), 10-15, 23-25, 27, 29, 31, 33-34, 36-37 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Claim(s) not searched:
20, 22

Reason for the limitation of the search:

Claim 20, referring to a compound identified by the method of claims 1-9 and not further defined, could not be searched. Claim 22, referring to the applications of compounds of claim 20, was not searched as well.



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number

EP 00 87 0316

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	N I TARASOVA ET AL.: "Inhibition of G-protein-coupled receptor function by disruption of transmembrane domain interaction" JOURNAL OF BIOLOGICAL CHEMISTRY. (MICROFILMS), vol. 274, no. 49, 3 December 1999 (1999-12-03), pages 34911-34915, XP002168073 AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD., US * the whole document *	1-39	
X	I N TARASOVA ET AL.: "Disruption of transporter protein function by transmembrane domain analogs" PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, SAN FRANCISCO, CALIFORNIA, USA, vol. 41, March 2000 (2000-03), page 398 XP001004628 * abstract *	1-39	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	WO 97 35881 A (GORDON NG ET AL.) 2 October 1997 (1997-10-02) * page 41 - page 44 *	1-39	
A	K-M COVITZ ET AL.: "Mutations that alter the transmembrane signalling pathway in an ATP binding cassette (ABC) transporter" EMBO JOURNAL., vol. 13, no. 7, 1994, pages 1752-1759, XP002178148 OXFORD UNIVERSITY PRESS, SURREY., GB ISSN: 0261-4189 * the whole document *	1-39	
	--- -/--		



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 87 0316

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	J A SHEPS ET AL.: "Hemolysin transport in Escherichia Coli " JOURNAL OF BIOLOGICAL CHEMISTRY. (MICROFILMS), vol. 270, no. 24, 16 June 1995 (1995-06-16), pages 14829-14834, XP002178149 AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD., US * the whole document *	1-39	
X	K-I KAWABATA ET AL.: "Protein interactions of Gtslp of Saccharomyces cerevisiae throughout a region similar to a cytoplasmic portion of some ATP-binding cassette transporters " EUROPEAN JOURNAL OF BIOCHEMISTRY, vol. 259, 1999, pages 112-119, XP002178150 BERLIN, DE ISSN: 0014-2956 * the whole document *	1-39	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
E	WO 01 36477 A (THE GOVERNMENT OF USA) 25 May 2001 (2001-05-25) * the whole document *	1-39	

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 00 87 0316

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

25-09-2001

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9735881	A	02-10-1997	AU	2020497 A	17-10-1997
			CA	2250567 A1	02-10-1997
			WO	9735881 A2	02-10-1997
			EP	0906339 A2	07-04-1999
WO 0136477	A	25-05-2001	AU	1922601 A	30-05-2001
			WO	0136477 A2	25-05-2001

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82